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ORIGINAL ARTICLE

The spectrum of nonadherence with medication in heart, liver, and lung tranplant patients assessed in various ways

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Summary

Adherence to medication regimes is crucial for transplant patients. Addressing methodological limitations and gaps in the literature, we studied: (i) the prevalence of nonadherence (NA) with immunosuppression (IS) using various measurement methods, (ii) NA prevalence regarding intake and timing, (iii) changes in NA over time, (iv) differences in NA across organ transplant populations, (v) NA regarding co-medication. Using a descriptive, prospective, comparative design over 3 months, we included convenience samples of adult heart (n = 79), liver (n = 55), and lung (n = 104) transplant patients. NA with IS was measured using self-report, collateral report, blood assay, electronic monitoring (Helping Hand™, Bang and Olufsen Medicom, Denmark), and their combinations. In the overall sample, depending on the method used, IS NA ranged from 23.9% to 70.0%. For co-medication, the overall NA rate was 30.1% using self-report. Nonadherence rates remained stable over time. At inclusion, significant NA differences between organ groups were reported via self- and collateral report; lung transplant patients were less adherent than heart or liver transplant recipients, both to IS and to co-medication.

Introduction

Following transplantation (Tx), adherence to medication regimens is crucial to prevent rejection, graft loss, and additional morbidity [1,2]. However, a recent meta-analysis indicated a nonadherence (NA) prevalence of immunosuppressants (IS) 22.6 cases per 100 patient-years (PPY) in solid organ Tx recipients [3].

Most studies on NA in Tx patients have substantial methodological limitations. First, the majority use a single NA measurement method; in the absence of a gold standard to assess medication NA, recent studies recommend a combination of assessment methods to enhance sensitivity [4,5]. Second, although evidence shows that the rate of medication NA is important, assessment methods rarely measure all dimensions of NA, i.e., taking, timing, dosing, and drug holidays. Third, most studies use cross-sectional designs, allowing no assessment of changes over time; optimally, adherence is assessed as a time dependent variable [3]. Fourth, while differences exist between Tx groups' NA rates, few studies directly compare NA among Tx populations [3]. Identifying adherence behavior differences between organ Tx groups will assist the development of organ specific adherence-enhancing interventions. Fifth, there is a paucity of NA data regarding co-medication. Tx patients typically manage multiple

co-morbidities requiring co-medications [6–10]. It is generally believed that nonadherence to co-medications is higher than to IS, but evidence supporting this hypothesis is currently lacking. Substantiating co-medication NA levels would close a relevant gap in Tx literature.

To deal with these issues, the aims of this study were as follows: (i) to determine, via combined measurement methods, the prevalence of IS medication NA, (ii) to assess NA prevalence regarding intake and timing of IS, (iii) to assess changes in IS NA over a 3-month period, (iv) to compare IS NA across adult heart, liver, and lung transplant recipients, (v) to measure co-medication NA and compare it between heart, liver, and lung Tx groups.

Materials and methods

Design, sample, and setting

We used a prospective, descriptive, comparative design, including baseline (T_0) and 3 month (T_1) (i.e., preintervention) follow-up data of the Medication Adherence Enhancing Study in Transplantation (MAESTRO), a randomized control trial testing the efficacy of adherence-enhancing interventions in transplant patients.

Participants were a convenience sample of adult heart, liver, and lung Tx recipients. They were all prescribed a twice-daily regimen of tacrolimus, undergoing regular (i.e., at least every 3–4 months) post-Tx follow-up at the University Hospitals in Leuven, Belgium, Dutch-speaking, and able to read, understand and signing our written informed consent form. Furthermore, to avoid interference with clinical medication trials and to allow time for IS therapy to stabilize, we included only patients more than 1 year post-Tx. Exclusion criteria were as follows: multi-organ transplants, caregiver management of the medication regimen, IS medication changes in the previous 4 weeks, mental impairment, terminal illness with a reasonable prospect of death in the next 3–6 months, being on the waiting list for re-transplantation, being pregnant or having the desire to become pregnant soon (pregnant patients have more frequent hospital follow-ups).

Variables and measurement

Demographics and clinical variables

Demographic data (i.e., age, gender, living situation, level of education, and professional status) were collected at the start of the study (T_0) via an interview using a structured questionnaire. The 'level of education' variable was operationalized following Appel *et al.* [11] comprising the following categories: 'primary/grade school', 'some high school', 'completed high school', 'some college/university', and 'completed college/university'. Professional status was identified using the following categories: 'full time', 'part time', 'unemployed', 'student', 'housewife/househusband', 'temporarily incapacitated to work', 'retired', and 'living on disability allowance'. In Belgium, all patients are covered by compulsory health insurance. The following clinical variables were retrieved from the medical files: organ transplanted (heart, liver, and lung); time after transplantation (in months); numbers and dosing frequencies of IS drugs; numbers and dosing frequencies of co-medications.

Nonadherence measurements

Self-report. At T_0 and T_1, self-reported IS medication NA data were collected in a patient interview using the 4-item Basel Assessment of Adherence with Immunosuppressive medication Scale (BAASIS) and the Visual Analog Scale (VAS) [12]. For the BAASIS, participants were asked in a nonthreatening, nonjudgmental manner about how often, over the last 4 weeks, they (i) had not taken their drugs (taking dimension), (ii) had taken their medication more than 2 h before or after their prescribed taking time (timing dimension), (iii) had skipped at least two consecutive doses of their drugs (drug holidays), (iv) had reduced the prescribed amount of their medication (dose reduction). Responses were given on a 6-point scale ranging from 0 (never) to 5 (every day). NA was defined as any self-reported NA (response score 1–5) on any of the 4 items [13]. In addition to individual scores for the taking and timing dimensions, we tabulated a total score for the four items. Then, patients indicated their adherence levels on the 120 mm Visual Analog Scale (VAS), ranging from no adherence (0 mm), to perfect adherence (100 mm), to taking more medication than prescribed (120 mm). For T_0 only, we also adapted the BAASIS to assess adherence to co-medications by replacing 'immunosuppressants' by 'co-medication = all medication except immunosuppressants' (Fig. 1). The performance of the BAASIS has been documented [12,14]. Validity of the VAS has been evaluated as described by Kerr *et al.* [15].

Collateral report. At T_0 and T_1, the treating physician and clinical nurse rated each patient's IS drug adherence on an ordinal scale as good, fair or poor. If either categorized the patient's adherence as less than 'good', the patient was classified as nonadherent. This measurement method has been successfully used previously in Tx patients [12].

Assay. The blood levels for tacrolimus were assessed as part of routine post-Tx follow-up care. The therapeutic range for tacrolimus varies according to the transplanted organ, the presence of kidney dysfunction, and other factors (e.g., combination with other immunosuppressants). Sub-therapeutic values were considered indicative of NA.

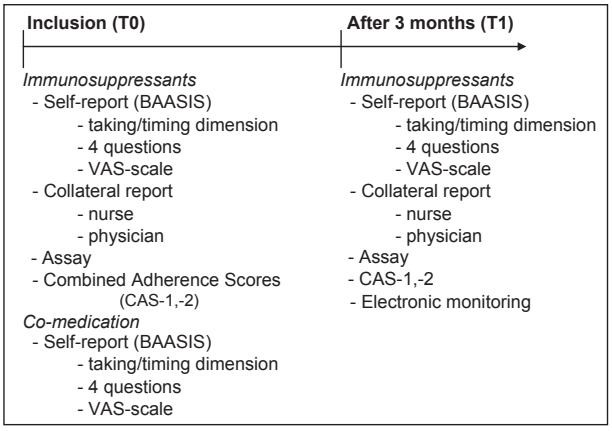

Figure 1 Overview of design and measurement methods.

Assay data were retrieved from the medical charts at T_0 and T_1.

Electronic monitoring (EM). Electronic monitoring captures patients' medication dynamics electronically via a microchip integrated in a pill bottle or blister package. Our study used the Bang & Olufsen Medicom Helping Hand™ Data Capture EM system (Fig. 2), which is specifically developed to assess adherence with drugs stored in blister packages and has been tested to ensure accuracy and reliability [16]. A microchip monitors presumable tablet intake by registering the date and time of each blister removal and reinsertion. Data are downloaded to a computer for analysis [17]. Four EM parameters were calculated: (i) taking adherence, percentage

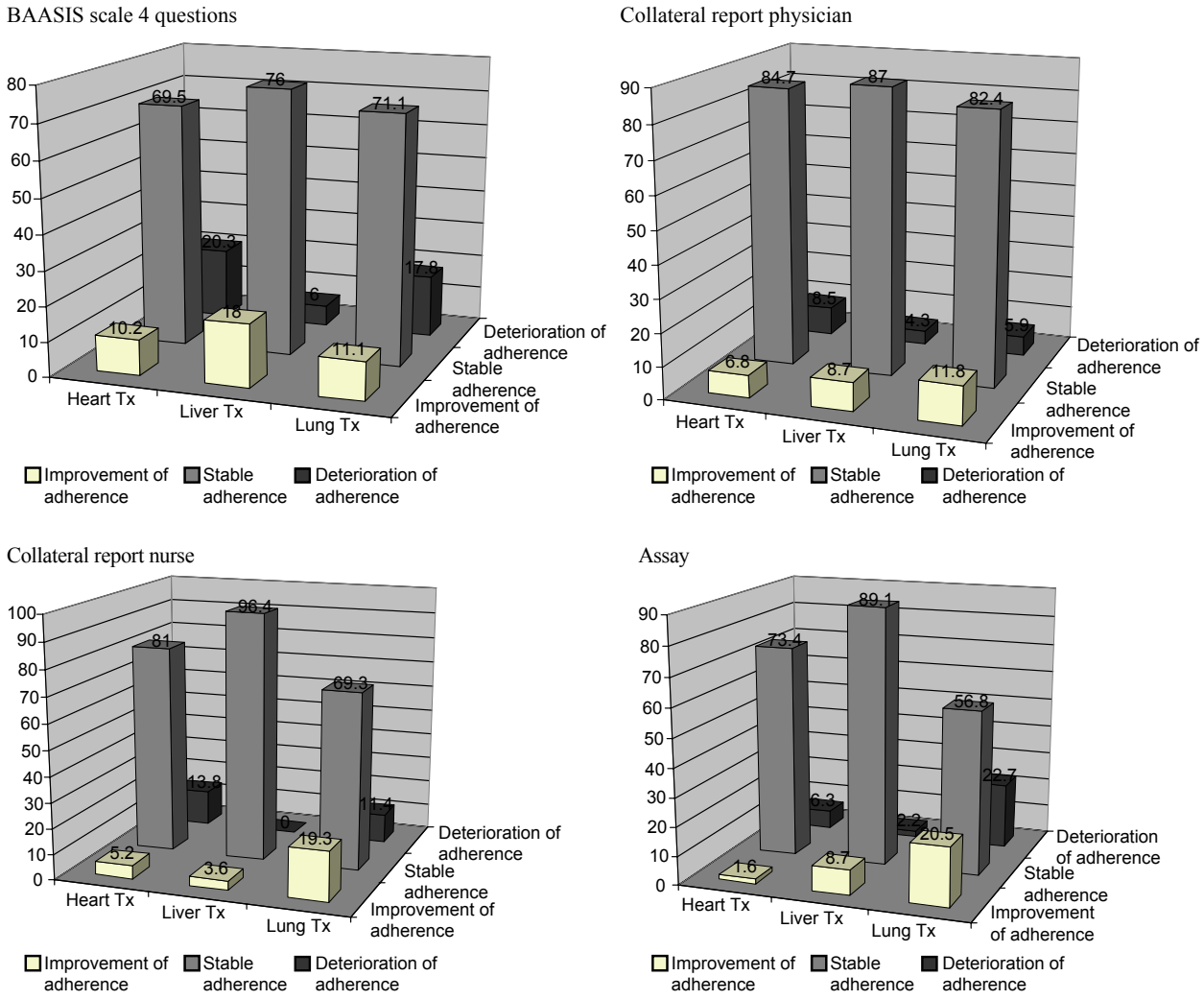

Figure 2 Evolution of prevalence of nonadherence in immunosuppressive medication over time.

of blister removals compared with the number prescribed for the monitoring period, (ii) dosing adherence, percentage of days on which the patient took the prescribed number of doses, (iii) timing adherence, percentage of correct dosing intervals (correct interval between two doses = ±2 h of prescribed intake timing), (iv) the number of drug holidays, no blister removals over a period greater than 24 h.

One presumed complication of EM use is a Hawthorne effect – i.e., enhanced performance of the monitored behavior resulting from users' awareness of being monitored – lasting 35–42 days [14,18,19]. Therefore, anywhere our data showed this effect we were prepared to disqualify that data from analysis. In addition, patients could report any deviations from the EM system, e.g., if they took their medication as prescribed but did not use the EM device. Such events were added to the EM data.

Composite adherence score (CAS). Two Composite adherence scores (CAS) were calculated, each based on data from multiple NA assessment methods. CAS-1 combined self-reported NA and collateral reports (physician and nurse combined) [12]. If either instrument showed nonadherence, the patient was classified as nonadherent. CAS-2 used self-reported NA, collateral-reported NA (physician and nurse combined), and nontherapeutic blood assay variability [12]. To calculate the CAS scores, the collateral reports of the physician and the nurse were combined. If either categorized the patient as less than 'good', the patient was categorized as nonadherent. Concerning assay, all sub-therapeutic levels were considered as nonadherent.

Procedure

Data collection took place between January 2008 and April 2009. Before the start of the study, the primary investigator (FD) trained 2 researchers – neither of whom belonged to the transplant team – in BAASIS interview techniques, i.e., methods to reliably assess self-reported NA. Eligible Tx recipients were approached during their scheduled outpatient clinic visits. Prior to that, they had been contacted by telephone to briefly explain the study. At T_0, after written informed consent was obtained, the BAASIS interview and the demographic questionnaire were completed. After the clinic visit, the researcher collected collateral NA data separately from the treating physician and the nurse in charge of the outpatient clinic; other relevant clinical and assay data were retrieved from participants' medical records.

All participants used the Helping Hand™ system for 3 months. If multiple dosages of tacrolimus were prescribed, only one was monitored via EM, with others taken as usual. To minimize disruption of patients' medicine-taking habits, those who usually used pillboxes were instructed to use them concomitantly with the EM system. All patients received oral and written instructions regarding correct EM use, as well as deviation report forms where patients could write down any remark concerning their medication intake [20,21]. All were informed that the EM system would monitor their medication intake dynamics.

After 3–4 months, during another scheduled outpatient visit (T_1), the BAASIS interview was repeated and EM data downloaded using the HelpView (Bang and Olufsen Medicom, Denmark) software. After this appointment, the researcher again collected collateral NA data separately from the physician and clinic nurse and assay data from the participants' medical records.

Approval of the ethics committee of the University Hospitals of Leuven, Belgium was obtained prior to the study (MC 4629).

Data analysis

For descriptive statistics regarding continuous variables, we explored data distributions and calculated median and quartile figures as appropriate. Nominal and ordinal data were expressed in absolute numbers and percentages. Adherence levels were compared per measurement method among the three organ groups using either the Kruskal–Wallis test for continuous data or the chi-squared test for nominal level data. Adherence changes over time were calculated via McNemar's test for nominal variables (e.g., the BAASIS, collateral report and assay) or the Wilcoxon signed-rank for continuous level data (e.g., VAS of the BAASIS). All calculations were performed using the SPSS® version 16.0 statistical software package (SPSS® Inc. Headquarters, Chicago, IL, USA). We considered a P-value of <0.05 statistically significant; two-sided tests were applied.

For descriptive purposes, EM parameters were expressed as continuous data. To indicate any Hawthorne effect, graphic analytic techniques were used to plot a nonlinear regression to represent the relationship between time and adherence [19]. Any period showing evidence of a Hawthorne effect was excluded from analysis.

Results

Sample

At the time of this study, MAESTRO researchers had invited 265 eligible heart, liver, and lung Tx recipients to participate, 238 (89.8%) of whom agreed to participate at T_0 (Fig. 3). Thirty-four (14.2%) participants dropped out

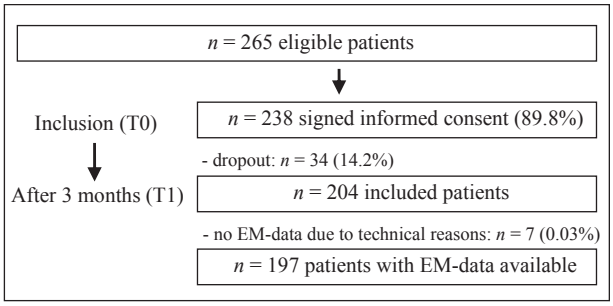

Figure 3 Flowchart of patient inclusion.

before T_1 and for 7 (0.03%) participants EM data were unavailable for technical reasons. Therefore, EM data were available in 197 patients at T_1. Table 1 details the final sample's demographic and clinical characteristics. Comparison of these data with those of patients who made their data available but otherwise declined participation ($N = 14$) indicated no significant differences (data not shown).

Prevalence of nonadherence

Self-report

At T_0, 36.7% of heart, 23.6% of liver, and 40.4% of lung Tx patients answered 'yes' to at least one of the four BAASIS questions (Table 2) and were therefore categorized as IS nonadherent. More detailed BAASIS analysis showed that 20.3% of heart, 12.7% of liver and 36.9% of lung Tx patients had forgotten to take their immunosuppressants at least once in the previous 4 weeks. Concerning timing, 26.6%, 20.0%, and 27.5% of heart, liver, and lung Tx patients, respectively, had taken their

Table 1. Demographic and clinical characteristics of the sample.

	Total (n = 238)	Heart (n = 79)	Liver (n = 55)	Lung (n = 104)	Significance
Gender (%)	138 (58.2)	53 (67.1)	32 (58.2)	53 (51)	* = 4.794
Male	138 (58.2)	53 (67.1)	32 (58.2)	53 (51)	P = 0.091
Median age (Q1–Q3)	58 (49–64)	59 (47–65)	62 (51–67)	56.5 (46.25–61)	H = 11.776
					P = 0.003
Do you live alone? (%)					
No	204 (85.7)	69 (87.3)	46 (83.6)	89 (85.6)	* = 0.319
Yes	34 (14.2)	10 (12.7)	9 (16.1)	15 (14.4)	P = 0.853
Level of education (%)					
Primary/grade school	4 (1.7)	0 (0)	2 (3.6)	2 (1.9)	* = 7.597
Some high school	94 (39.3)	26 (32.9)	24 (42.9)	44 (42.3)	P = 0.474
Completed high school	68 (28.5)	25 (31.6)	16 (28.6)	27 (26)	
Some college/university	20 (8.4)	7 (8.9)	2 (3.6)	11 (10.6)	
Completed college/university	53 (22.2)	21 (26.6)	12 (21.4)	20 (19.2)	
Employment (%)					
Full time	20 (8.4)	8 (10.1)	3 (5.4)	9 (8.7)	* = 36.817
Part time	19 (7.9)	7 (8.9)	1 (1.8)	11 (10.6)	P = 0.001
Unemployed	1 (0.5)	0 (0)	0 (0)	1 (1.2)	
Student	4 (2)	3 (4.7)	0 (0)	1 (1.2)	
Housewife/househusband	16 (8)	8 (12.5)	5 (9.6)	3 (3.6)	
Incapacitated to work	23 (11.5)	12 (18.8)	5 (9.6)	6 (7.1)	
Retired	75 (37.5)	27 (42.2)	27 (51.9)	21 (25)	
Living on disability allowance	80 (40.2)	14 (21.9)	14 (27.5)	52 (61.9)	
Median time living with graft (months) (Q1–Q3)	46 (21.5–78)	51 (22–80)	30.5 (15–73)	57 (33.7–76.2)	H = 8.651
					P = 0.013
Number of different immunosuppressive drugs (%)					
1	17 (7.1)	2 (2.5)	14 (25)	1 (1)	H = 98.552
2	133 (55.9)	67 (84.8)	37 (67.2)	29 (27.9)	P = 0.001
3	86 (36)	10 (12.7)	3 (5.4)	73 (70.2)	
4	1 (0.4)	0 (0)	0 (0)	1 (1)	
Median number of nonimmunosuppressive drugs (Q1–Q3)	4 (3–5)	2 (3–5)	3 (2–5)	8 (6–11)	H = 106.356
					P = 0.001
Median number of medication doses/day (IS and nonIS) (Q1–Q3)	3 (2–4)	2 (2–3)	3 (2–3.)	3.5 (3–5)	H = 29.740
					P = 0.001

*Fischer's Exact test.
H, Kruskal–Wallis test.

Table 2. Prevalence of nonadherence in immunosuppressive medication.

BAASIS scale	Total	Heart Tx	Liver Tx	Lung Tx	Statistics	*P*-value
Taking dimension						
Nonadherent T_0 (%)	36/237 (15.2)	16/79 (20.3)	7/55 (12.7)	13/103 (12.6)	$\chi^2 = 2.359$	0.308
Nonadherent T_1 (%)	22/202 (10.9)	4/60 (5.1)	8/49 (14.5)	10/93 (10.8)	$\chi^2 = 2.597$	0.273
P-value McNemar test	0.110	0.039	1.000	0.581		
Timing dimension						
Nonadherent T_0 (%)	70/237 (29.5)	21/79 (26.6)	11/55 (20.0)	38/104 (36.5)	$\chi^2 = 5.413$	0.067
Nonadherent T_1 (%)	58/198 (29.3)	14/59 (17.7)	15/49 (27.3)	29/90 (27.9)	$\chi^2 = 1.296$	0.523
P-value McNemar test	0.590	0.607	0.454	0.307		
Four questions						
Nonadherent T_0 (%)	84/238 (35.3)	29/79 (36.7)	13/55 (23.6)	42/104 (40.4)	$\chi^2 = 5.988$	0.200
Nonadherent T_1 (%)	69/201 (34.3)	17/59 (28.8)	19/50 (38.0)	33/92 (35.9)	$\chi^2 = 2.436$	0.656
P-value McNemar test	0.643	0.238	0.146	0.500		
VAS						
T_0 Median (Q1–Q3)	95.0 (85.0–100)	90.0 (80.0–100)	92.5 (85.0–100)	95.0 (90.0–100)	H = 34.620	**0.011**
Minimum–Maximum	11–105	50–105	50–100	11–100		
T_1 Median (Q1–Q3)	90.0 (80.0–100)	90.0 (82.5–100)	90.0 (80.0–99.0)	95.0 (80.0–100)	H = 19.435	0.494
Minimum–maximum	10–110	55–105	50–100	10–110		
Wilcoxon test; *P*-value	Z = −2.479; **0.013**	Z = −0.567; 0.571	Z = −1.447; 0.148	Z = −2.143; **0.032**		
Collateral report Physician						
Nonadherent T_0 (%)	56/234 (23.9)	18/79 (22.8)	6/53 (11.3)	32/102 (31.4)	$\chi^2 = 7.789$	**0.020**
Nonadherent T_1 (%)	46/194 (23.7)	10/59 (16.9)	7/48 (14.6)	29/87 (33.3)	$\chi^2 = 8.155$	**0.017**
P-value McNemar test	0.362	1.000	0.687	0.302		
Collateral report Nurse						
Nonadherent T_0 (%)	69/221 (31.2)	34/79 (43.0)	1/39 (2.6)	34/103 (32.7)	$\chi^2 = 24.106$	**0.001**
Nonadherent T_1 (%)	57/178 (32.0)	21/58 (36.2)	1/31 (3.2)	35/89 (39.3)	$\chi^2 = 14.457$	**0.001**
P-value McNemar test	0.749	0.227	/*	0.248		
Assay						
Nonadherent T_0 (%)	57/235 (24.3)	17/78 (21.8)	9/55 (16.4)	31/102 (30.4)	$\chi^2 = 4.212$	0.122
Nonadherent T_1 (%)	51/192 (26.6)	14/63 (22.2)	9/42 (21.4)	28/87 (32.1)	$\chi^2 = 2.585$	0.275
P-value McNemar test	0.771	0.375	0.375	0.108		
CAS-1						
Nonadherent T_0 (%)	136/226 (60.2)	53/79 (67.1)	18/44 (40.9)	65/103 (63.1)	$\chi^2 = 8.760$	**0.013**
Nonadherent T_1 (%)	111/200 (55.5)	29/59 (49.2)	25/51 (49.0)	57/90 (63.3)	$\chi^2 = 4.066$	0.131
P-value McNemar test	0.590	0.064	0.388	1.000		
CAS-2						
Nonadherent T_0 (%)	159/227 (70.0)	60/79 (75.9)	25/45 (55.6)	74/103 (71.8)	$\chi^2 = 5.974$	**0.050**
Nonadherent T_1 (%)	136/204 (66.7)	39/65 (60.0)	32/49 (65.3)	65/90 (72.2)	$\chi^2 = 2.591$	0.274
P-value McNemar test	0.382	**0.031**	0.549	1.000		
Electronic monitoring						
Mean % taking nonadherence (min–max)	10.6 (7–119)	8.4 (24–103)	9.7 (33–119)	13 (7–102)	H = 34.775	0.663
Mean % timing nonadherence (min–max)	19.8 (1–100)	15.6 (7–100)	19.2 (1–100)	22.6 (1–99)	H = 44.053	0.385
Mean % dosing nonadherence (min–max)	12.7 (2–100)	9.5 (30–100)	12.6 (2–100)	14.8 (7–99)	H = 65.011	0.218
Mean % drug holidays (min–max)	1.3 (0–20)	1.5 (0–20)	1.0 (0–16)	1.39 (0–18)	H = 11.583	0.640

*Computed only for a PXP table, where P must be greater than 1. Bold indicates statistically significant ($P < 0.05$).
BAASIS, basel assessment of adherence with immunosuppressive medication scale; CAS, composite adherence scores; χ^2, chi-squared test; H, Kruskal–Wallis test; Tx, transplant; VAS, visual analog scale; Z, Wilcoxon signed rank test.

medication more than two hours earlier or later than the prescribed time. The median VAS scores at T_0 were 90.0, 92.5, and 95.0 for heart, liver, and lung Tx patients, respectively.

At T_1, taking the answers of the four questions into consideration (see operational definitions), 28.8%, 38.0%, and 35.9% of heart, liver, and lung Tx patients, respectively, reported nonadherence. For the taking dimension,

5.1% of heart, 14.5% of liver and 10.8% of lung Tx patients were nonadherent. For timing, 17.7%, 27.3% and 27.9% of heart, liver, and lung Tx patients, respectively, reported nonadherence. On the VAS, heart and liver Tx patients' median score was 90.0; lung Tx patients' median score was 95.0.

During the T–T_1 interval, adherence improved in 73 patients' (40.6%), it remained stable in 61 (33.9%) and 46 patients (25.6%) became nonadherent. Differences between organ groups are detailed in Fig. 2.

Collateral reports

At T_0, the physicians estimated that 22.8% of heart, 11.3% of liver, and 31.4% of lung Tx patients were nonadherent (Table 2). At T_1, collaterally reported NA rates were 16.9%, 14.6%, and 33.3% for heart, liver, and lung Tx populations, respectively. During the 3-month period between T_0 and T_1, 18 patients (9.5%) became adherent, 160 (84.2%) remained stable and 12 (6.3%) became nonadherent in the opinions of the treating physicians (Fig. 2).

Nurses estimated that 43.0% of heart, 2.6% of liver and 32.7% of lung Tx patients were NA at T_0. At T_1, these results were 36.2%, 3.2%, and 39.3%, respectively (Table 2). That is, nurses estimated that 21 patients (12.1%) had improved, 135 (77.6%) had remained stable and 18 (10.3%) had become nonadherent during the 3-month period between T_0 and T_1 (Fig. 2).

Assay

At T_0, 21.8% of heart, 16.4% of liver and 30.4% of lung transplant patients were categorized as nonadherent using the assay method (Table 2). At T_1, nonadherence rates were respectively 22.2%, 21.4%, and 32.1% for the heart, liver, and lung populations (Fig. 2).

Electronic monitoring

The EM data showed no potential Hawthorne effect (data not shown). Therefore, all EM-data from the 3-month observation period were included. For the total study sample, the median 3-month prevalences of EM nonadherence were as follows: 10.6% taking, 19.8% timing, 12.7% dosing, and 1.3% drug holidays. Differences between organ groups are shown in Table 2.

Composite adherence scores

At T0, 67.1% of heart, 40.9% of liver, and 63.1% of lung Tx patients were classed nonadherent by CAS-1 (Table 2). At T_1, NA figures for heart, liver, and lung Tx patients were 49.2%, 49.0%, and 63.3%, respectively. Using the CAS-2 algorithm at T_0, 75.9% of heart, 55.6% of liver, and 71.8% of lung Tx patients were categorized as nonadherent (Table 2). At T_1, the CAS-2 NA rates were 60.0%, 65.3%, and 72.2% for heart, liver, and lung Tx patients, respectively.

Differences in nonadherence between T_0 and T_1

In self-report, collateral report, assay, and composite scores, only two significant differences in NA were observed between T_0 and T_1 (Table 2). On the VAS, lung Tx patients rated themselves significantly less adherent to their IS medication at T_1 than at T_0; and for CAS-2, heart Tx patients showed increased NA at T_1 (Table 2). Figure 2 shows the proportions of patients whose adherence scores improved, remained stable, or deteriorated.

Differences in nonadherence between organ Tx populations

Comparison of NA in the three studied Tx populations' showed significant differences in only four parameters. Whereas, at T_0, the BAASIS VAS scale depicted heart Tx patients as significantly less adherent than liver or lung Tx patients, physicians' collateral reports at both T_0 and T_1 ranked lung Tx patients as least adherent, also by a significant margin. At the high end of the adherence scale, while nurses' collateral reports ranked liver Tx patients as significantly more adherent than either other group both at T_0 and T_1, CAS-1 and CAS-2 adherence scores were highest for liver Tx patients only at T_0.

Differences in nonadherence between immunosuppressants and co-medication

For co-medication, the four BAASIS questions revealed NA in 53.4% of lung Tx participants (Table 3) – significantly higher than in the heart (39.2%) or liver (21.4%) Tx groups. The VAS figures confirmed this ranking, with median NA scores of 91.0 for heart, 90.0 for liver, and 95.0 for lung Tx patients.

Comparing the BAASIS's IS taking dimension figures with those reported for co-medication indicated significantly more nonadherence to co-medication ($P = 0.002$), although the BAASIS timing dimension showed no significant difference ($P = 0.375$). VAS results also showed significantly more nonadherence ($P = 0.043$) to co-medication.

Discussion

The prevalence of nonadherence

This study is the first to present NA to IS regimens in heart, liver, and lung Tx patients using four different

measurement methods and two combined scores. The different measurement methods showed a wide range of results, with the overall sample's NA figures in ranging from 23.9% to 70.0%. In all three groups, however, the highest NA rates were found using CAS-1, CAS-2, and electronic monitoring, confirming that combined measurement methods produce a more complete view of patients' NA [4].

Electronic monitoring data analysis indicated a mean 3-month NA prevalence of 10.6% for taking, 19.8% for timing, 12.7% for dosing, and 1.3% for drug holidays. These rates differed substantially from those of Butler *et al.* [22], according to whom 45% of subjects were nonadherent during the monitored period, while 12% and 26% missed at least 20% and 10% of days, respectively.

We can offer three possible explanations for such pronounced differences. First, different transplant populations were investigated: Butler [22] included kidney Tx recipients, who generally show higher NA rates than any of our three subject groups [3]. Second, cultural differences and health system factors may have played a role [21.] Third, different EM devices were used: Butler [22] used the MEMS®-V TrackCap EM system (Aardex, Ltd., Zug, Switzerland); we used the Helping Hand™. A recent laboratory evaluation study showed error-free operation in 70–87% of Helping Hand™ devices, compared with 20–100% of MEMS, depending on battery life [16].

Nonadherence differences between immunosuppressants and co-medication

The BAASIS taking NA figures were significantly higher for co-medication than for immunosuppressants ($P = 0.002$), suggesting that, while patients are clearly aware that immunosuppressants are crucial to their health, they attribute less importance to co-medication. Concerning the BAASIS timing dimension, patients experience many problems taking both immunosuppressants (29.5%) and co-medication (30.1%) regularly. Focusing on specific adherence dimensions is particularly important for populations in which even slight deviations from dosing schedules can influence clinical outcomes (e.g., transplant or HIV) [14,20]. For healthcare professionals working with such groups, developing and integrating adherence-enhancing interventions – focusing both on taking and timing – demands a high priority [23–25].

Measurement of nonadherence at T_0 and T_1

Between T_0 and T_1, both VAS results in lung Tx patients and CAS-2 results in heart Tx patients showed significant changes. As the principle of the Hawthorne effect suggests that EM alone will lead to significant temporary improvements in patients' medication adherence [18], we tested our data for evidence of such an effect. We found none. This agrees with Dunbar-Jacob's observation that, over a short term (3 months), barring major events, medication adherence is a relatively stable behavior [26]. However, it contradicts Deschamps *et al.* [18] who concluded that EM had positively influenced the medication taking behavior of 26% of their study participants. Two other studies, one in patients with hypertension and one in alcohol dependent patients, demonstrated, respectively, that using EM alone improved blood pressure and decreased alcohol consumption [27,28].

Comparison of nonadherence between organ Tx populations

Of our three Tx populations, lung Tx recipients showed the highest NA figures, both for IS and nonIS medication. The lung Tx patients were also significantly younger, had longer post-transplant courses, used both more IS and

Table 3. Prevalence of nonadherence in co-medication.

BAASIS scale	Total	Heart Tx	Liver Tx	Lung Tx	Statistics	*P*-value
Taking dimension						
Nonadherent for taking T_0 (%)	49/229* (21.4)	14/77 (17.7)	7/50 (12.7)	28/102 (27.5)	$\chi^2 = 4.323$	0.115
Timing dimension						
Nonadherent for timing T_0 (%)	69/229* (30.1)	21/77 (26.6)	11/50 (20.0)	37/102 (36.3)	$\chi^2 = 3.698$	0.157
Four questions						
Nonadherent T_0 (%)	97/229* (42.3)	31/77 (39.2)	11/50 (22.0)	55/102 (53.4)	$\chi^2 = 13.818$	**0.008**
VAS scale						
Nonadherent T_0 Median (Q1–Q3)	95.0 (85.0–100)	91.0 (80.0–100)	90.0 (85.0–100)	95.0 (85.0–100)	H = 24.635	0.173
Minimum–Maximum	10–105	50–105	50–100	10–105		

*Not all patients take co-medication. Bold indicates statistically significant ($P < 0.05$).
BAASIS, basel assessment of adherence with immunosuppressive medication scale; χ^2, chi-squared test; H, Kruskal–Wallis test; Tx, transplant; VAS, visual analog scale.

more co-medication, and required more doses per day than either other group. Previous studies have confirmed that these factors increase the likelihood of NA [3,29,30]. Moreover, our analyses showed that higher numbers of medication doses per day may increase medication NA, as the two increased together [29].

Comparison of physicians' and nurses' nonadherence ratings

Physicians' collateral NA reports differed substantially from nurses': in heart Tx patients, the nurses rated more patients as nonadherent than did physicians; for the liver Tx group, the reverse was observed. For lung Tx recipients, nurses' and physicians' appraisals were more equal. In any case, though, Miller *et al.* [31] stated that clinicians tend to overestimate medication adherence, thereby missing important intervention opportunities.

The lowness of nonadherence rates perceived by nurses in liver Tx patients probably relates to the way follow-up is organized for this group in this study's Tx centre. Heart and lung Tx follow-ups are conducted by specialized nurses who know them well. However, liver Tx patients receive follow-ups from a study nurse who knows only those patients included in clinical trials and who usually meets with them only shortly before and after transplantation. This lack of long-term contact might have biased the nurses' NA estimates. The observed differences between physicians and nurses highlight the value of combining several healthcare workers' NA assessments. Conversely, collateral reporting by a single person is regarded as an invalid method of assessing medication NA [12,31,32]. In the calculation of CAS-1 and CAS-2, the scores of the physicians' and nurses' collateral reports were combined to give more balanced NA assessments in every patient group.

Limitations of the study

This study was subject to certain identifiable shortcomings. First, selection bias was possible, as more nonadherent patients may have declined participation in the study than adherent ones. In view of clinical and demographical data, we compared included patients with those who consented to use their data but who declined further participation ($N = 14$). However, no significant differences were found.

Second, although the study participants used as many as four IS medications, we assessed patients' adherence to tacrolimus alone. As NA may differ between medications, our findings might not reflect the patients' overall IS adherence. From studies in HIV, we know that NA was comparable between antiretrovirals [33]. However, future studies should test this principle in Tx patients.

Third, the researchers who interviewed the patients also participated in data input, i.e., the measurements were not necessarily blind to the investigators. To avoid potential influences, the BAASIS interviews were scheduled first. Data from assay, collateral report, and EM were obtained afterwards. Hence, it is less likely that the lack of blinding affected our results.

Fourth, this study was conducted in one tertiary care centre in Belgium. Centre-specific aspects, cultural characteristics, and aspects of the Belgian healthcare system, e.g., the compulsory health insurance system, might have affected the results. Therefore, the findings of this study cannot be generalized as such to the entire Tx population of the Western world.

To conclude, we investigated the prevalence of NA to IS medication, using triangulation, changes in NA over time, differences in NA across organ Tx populations, and NA to co-medication in adult heart, liver, and lung transplant patients. In the overall sample, NA to IS ranged from 23.8% (T_0 physician collateral report) to 70.0% (T_0 CAS-2). The collated results indicated that patients' adherence rates remained stable over time. Lung Tx patients were less adherent than heart or liver Tx recipients and showed more NA to co-medication than to IS. Future NA studies should cover different organ Tx populations, investigate NA to both IS and nonIS medication. Triangulation via multiple measurement instruments is imperative to detect nonadherence with the greatest possible sensitivity.

Authorship

DBL: designed research/study, performed research/study, collected data, analyzed data, and wrote the paper. DF: designed research/study, performed research/study, collected data, and critically revised the article. BL: collected data, responsible for the critical revision of article. VJ, VG, and NF: responsible for critical revision of article. DGS: designed research/study, performed research/study, analyzed data, wrote paper, and critical revision of article.

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