

# Patient-reported and Physician-estimated Adherence to HAART

## Social and Clinic Center-related Factors Are Associated with Discordance

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**OBJECTIVES:** To evaluate the rate of discordance between patients and physicians on adherence to highly active antiretroviral therapy (HAART) and identify factors related to discordance in these two assessments.

**DESIGN:** Prospective, multicenter, cohort study (AdICoNA) nested within the Italian Cohort Naïve Antiretrovirals (ICONA) study.

**SETTING:** Tertiary clinical centers.

**PARTICIPANTS:** The patients filled out a 16-item self-administered questionnaire on adherence to HAART. At the same time, physicians estimated the current HAART adherence of their patient.

**MAIN OUTCOME MEASURE:** Discordance between patient and physician on adherence to antiretroviral therapy.

**RESULTS:** From May 1999 to March 2000, 320 paired patient-physician assessments were obtained. Patients had a mean plasma HIV RNA of 315 copies/ml (64% had undetectable HIV RNA) and a mean CD4+ cell count of 577 cells  $\times$  10<sup>6</sup>/L. Nonadherence was reported by 30.9% of patients and estimated by physicians in 45.0% cases. In 111 cases (34.7%), patients and physicians were discordant on adherence to HAART. Kappa statistics was 0.27. Using patient-assessed adherence as reference, sensitivity, specificity, positive predictive value, and negative predictive value of physician-estimated adherence were 64.7%, 66.6%, 81.2%, and 45.8%, respectively. On multivariable analysis, low education level, unemployment, absence of a social worker in the clinical center, and unavailability of afternoon visits were significantly correlated with patient-physician discordance on adherence to antiretrovirals.

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**CONCLUSIONS:** Physicians did not correctly estimate patient-reported adherence to HAART in more than one third of patients. Both social variables and factors related to the clinical center were important predictors of discordance between patients and physicians. Interventions to enhance adherence should include strategies addressed to improve patient-physician relationship.

**KEY WORDS:** compliance; AIDS/HIV; doctor-patient relationship; quality of care; health care service.

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Adherence to medications is crucial to effective therapy. For chronic conditions, long-term and sometimes complex regimens make it critical to sustain adherence over time. In HIV-infected populations, nonadherence to antiretrovirals has been demonstrated to be one of the most important predictors of therapeutic failure.<sup>1-6</sup> Suboptimal adherence can also lead to the development and spread of multi-drug-resistant HIV strains.<sup>7</sup>

In the clinical management of HIV, decisions to start or to change therapy, and type of therapeutic regimen, may be decided by screening patients for adherence.<sup>8</sup> A recent study demonstrated that the maximal benefit from genotype-guided treatment was obtained in adherent patients.<sup>9</sup> However, to date, there is no gold standard for measuring adherence. Several methods to assess adherence, such as patient self-report, electronic monitoring systems, and pill count have shown acceptable validity and feasibility.<sup>4,10,11</sup> In clinical practice, adherence assessments are often rendered by the physician. Nevertheless, several studies have suggested that physicians are poor at judging whether or not patients are taking their medications,<sup>4,12,13</sup> both in the short term and longer term.<sup>14</sup> Poor concordance between patient and physician reports of adherence might lead to inappropriate decisions regarding therapy. There are few studies primarily designed with the objective of assessing the concordance on adherence to drugs between HIV-infected patients and physicians, and no published studies have evaluated factors that are related to a less accurate physician assessment of patient-reported adherence.

We performed this study to assess the degree of discordance between patients and physicians on adherence to highly active antiretroviral therapy (HAART) and to identify factors related to discordance in these assessments.

## STUDY POPULATION AND METHODS

### Study Design and Sample

AdICONA is a prospective, multicenter cohort study aimed at assessing issues related to medication adherence in persons with HIV infection initiating HAART.<sup>15</sup> AdICONA is nested within a larger study, the Italian Cohort Naïve Antiretrovirals (I.CO.N.A),<sup>16</sup> a 65-center observational study on the natural history of HIV disease among adult persons previously naïve to antiretroviral drugs. A total of 3,586 individuals were enrolled in the cohort after providing written informed consent. Sociodemographic and clinical characteristics as well as clinical events and therapeutic changes are collected at each follow-up visit or at least every 6 months and recorded directly to an on-line computerized database ([www.icona.org](http://www.icona.org)). Stage of HIV disease was defined according to the 1993 Centers for Disease Control classification: people having had an AIDS-related disease were considered at a more advanced stage of HIV disease. In Italy, a national health care system provides universal medical care including drugs to HIV-infected people. This is the optimal setting to study the determinants of adherence without having any confounder from financial aspects.

A total of 23 clinical centers agreed to participate in this study on adherence to drugs and enrolled all consecutive patients seen for follow-up visits in I.CO.N.A. Enrollment took place from May 1999 to March 2000. The inclusion criterion was receiving HAART, including at least one protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI), for at least 1 month. Exclusion criteria were inability to complete the questionnaire, delirium or dementia, and hospitalization at the time of enrollment.

### Patient-assessed Adherence Measure

Participants in the study were asked to complete a 16-item self-administered questionnaire previously tested in another Italian HIV-infected patient population.<sup>17</sup> Adherence to HAART is assessed in the questionnaire by asking the last time the patient forgot to take therapy (response options include “yesterday,” “last week,” “more than 1 week but less than three weeks ago,” “within 3–4 weeks ago,” and “never”). The questionnaire also investigates knowledge about the current HAART scheme, reasons for nonadherence, interruptions in drug supply, beliefs about treatment, perceived health status, psychological well-being (using the Mental Health Index-5 [MHI-5]<sup>18</sup>), social support, symptoms, satisfaction with health care, use of alcohol or recreational drugs, level of education, type of housing, type of profession, length of unemployment, and monthly income. Satisfaction with health care was measured in the questionnaire using a single-item visual analogue scale ranging from 0 (lowest satisfaction) to 100 (highest satisfaction). On average, 10 minutes are required to fill out the questionnaire. Questionnaires were collected in anonymous sealed envelopes and delivered to the data center.

### Physician-assessed Adherence Measure

Immediately before the visit, physicians were asked to complete a single-item questionnaire estimating the patient's current adherence to antiretroviral therapy (response options included “optimal,” “suboptimal,” and “absent”). At the time of answering the questionnaire, physicians did have access to prior HIV RNA values in the medical record.

### Characteristics of the Clinical Centers

Before starting enrollment in AdICONA, a standardized survey was administered by mail to a clinical investigator at each clinical center. The survey assessed care characteristics of the center, the number of outpatients being followed, number of patients daily seen by each physician, whether patients are generally seen by the same physician, whether patients can also be seen both mornings and afternoons, and whether a psychologist and/or a social worker are available in the center. We also considered geographic location of the center and whether it is an academic medical center.

### Statistical Analysis

The main hypothesis was that the degree of discordance between patient-reported and physician-estimated adherence would be relevant. Moreover, we hypothesized that care characteristics of clinical centers might be associated with discordance on adherence to drugs between patients and physicians.

A descriptive analysis of the study population was performed. Homogeneity was confirmed between the AdICONA and the I.CO.N.A. study populations, and between responding and nonresponding AdICONA participants. Data on reasons for refusing to take the survey were not collected.

Patient-reported adherence to HAART was used as the reference for adherence measurement and defined by asking the last time the patient forgot to take therapy. Based on the responses, patients were classified as “nonadherent” (having forgotten to take a dose of therapy “yesterday” or “last week”) versus “adherent” (having forgotten a dose “more than 1 week but less than 3 weeks ago,” “within 3–4 weeks,” or “never”). By asking the patient the last time he or she forgot to take therapy, we could not distinguish the adherence to all the different drugs of the same dose. According to the physician-estimated adherence, patients were classified as “optimally adherent” versus “suboptimally” or “nonadherent.” It should be noted that the categorization of both the patients' and physicians' responses are arbitrary and, to date, there is no consensus on which is the more appropriate in capturing the nonadherent group of patients. For these reasons, we also showed the distribution of all the complete response options on adherence by both patients and physicians.

Concordance on adherence between patients and physicians was evaluated using a  $\kappa$  statistic to test for level

of agreement beyond chance. Cohen's  $\kappa$  measures the agreement between the evaluations of two raters when both are rating the same object. A value of 1 indicates perfect agreement. A value of 0 indicates that agreement is no better than chance. If a  $\kappa$  value is below 0.40 the agreement is considered very poor. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of physicians' assessment of adherence were also calculated.

The relationship of various dichotomized factors to discordance between patients and physicians was compared using a  $\chi^2$  test and odds ratios (OR) with 95% confidence intervals (95% CI). Continuous variables were analyzed employing the Student's *t* test. A *P* value of less than .05 was considered statistically significant.

Multivariable analysis was performed using a multiple logistic regression in which the dependent variable was the discordance on adherence between patients and physicians, adjusting for clinical center and all variables found to be significantly (*P* < .05) associated with the dependent variable at bivariate analysis.

## RESULTS

Among 385 qualifying patients enrolled in I.CO.N.A. at the 23 participating clinical centers between May 1999 and March 2000, 358 (93%) completed the questionnaire. Twenty-seven persons refused to participate. The item-missing rate of the patient questionnaire ranged from 0.8% to 4.7%. Physicians' participation rate was 89.4%; physicians in two clinical centers were not able to participate at all due to time constraints. The final number of paired patient-physician adherence assessments was 320.

Table 1 shows the characteristics of the 320 patients eligible for the analysis. Eligible patients had a mean age of 36 years, 29% were female, 36% reported injection drug use as their HIV transmission mode, 23% were men who had sex with men, and 36% reported heterosexual intercourse. Forty-six percent of participants had an educational level of less than 8 years and 17% had an income of less than \$350 (388 Euro)/month. Twenty-one percent of individuals were unemployed. Sixty-four participants had had an AIDS-defining event in their medical history. Median plasma HIV RNA was 99 copies/ml (interquartile range [IQR], 80–562) and mean CD4+ cell count was 576 cells  $\times 10^6/L$  (standard deviation [SD],  $\pm 345$ ). Overall, patients had received antiretroviral therapy for a mean of 1.6 years (SD  $\pm 0.64$ ) and had been on the current HAART regimen of 3 drugs for a mean of 1 year (SD  $\pm 0.68$ ). More than half (57%) of participants had switched from their first HAART regimen.

Of the 23 participating clinical centers, 52% were academic medical centers, 30% were located in the north of Italy, 57% in the middle, and 13% in the south. In 48% of centers, patients were seen always by the same physician and in 46% people could also be seen in the afternoons. A psychologist was available in 22% and a social worker in 39% of centers. In 44% of centers, the total number of

**Table 1. Characteristics of the AdICONA Participants and of the Participants Eligible for This Analysis (N = 320)**

Patient-related characteristics	
Gender, n (%)	
Male	227 (71)
Female	93 (29)
Mean age, y (range)	36.4 (19 to 66)
<35, n (%)	153 (48)
HIV transmission mode, n (%)	
Injection drug use	116 (36)
Men having sex with men	71 (23)
Heterosexual intercourse	116 (36)
Receipt of blood products	14 (4)
Unknown	3 (1)
Level of highest education, n (%)	
$\leq 8$ years	148 (46)
9 to 13 years	117 (37)
University	33 (10)
Unknown	22 (7)
Income/month, n (%)	
<\$350/<Euro 388	56 (17)
\$350 to \$1250/Euro 388–1293	151 (47)
>\$1250/>Euro 1293	50 (16)
Unknown	63 (20)
Unemployment, n (%)	67 (21)
Unknown	46 (14)
Homelessness, n (%)	8 (2.5)
Self-reported alcohol use	42 (13)
Self-reported recreational drugs use	24 (7.5)
HIV-related variables	
Previous AIDS-related event, n (%)	64 (20)
HIV RNA copies/ml, median (IQR)	99 (80 to 562)
<500 copies/ml, n (%)	206 (64)
Mean CD4+ cell count $\times 10^6/L$ (SD)	576 (345)
<200, n (%)	36 (11)
Treatment-related variables	
Years on antiretroviral therapy	
Overall, mean (SD)	1.6 (0.64)
On last HAART scheme, mean (SD)	1.0 (0.68)

IQR, interquartile range; SD, standard deviation, HAART, highly active antiretroviral therapy.

patients being seen was greater than 500. Median of patients seen daily by each physician was 7 (25th to 75th percentile: 4 to 9).

Ninety-nine patients (30.9%) self-reported nonadherence and were more likely to have a detectable HIV RNA (OR, 1.85; 95% CI, 1.05 to 3.13; *P* = .03) than those reporting adherence. Physicians estimated nonadherence in 144 (45.0%) of their patients. The odds of being estimated nonadherent by physicians for people with detectable HIV RNA was 2.21 (95% CI, 1.27 to 3.86; *P* = .004) relative to people with undetectable HIV RNA. Because categorization of both patients' and physicians' responses we have chosen were arbitrary, we show in Table 2 the relationship between the complete options of the patient's estimate of adherence and those of physicians.

In 143 of 320 cases (44.7%) patients and physicians agreed on adherence, and in 66 cases (20.6%) they agreed on nonadherence. In 33 cases (10.3%) patients reported

**Table 2. Relationship Between Patient's Estimate of Adherence Question and the Physician's Estimate of Adherence**

			Patient's Report on the Last Time He/She Forgot to Take Therapy				
			Yesterday	Last Week	>1 but <3 Weeks Ago	3 to 4 Weeks Ago	Never
			NonAdherent		Adherent		
Physician's estimate of adherence	Optimal	Adh	8 (23.5)	25 (38.5)	27 (55.1)	36 (65.5)	80 (68.4)
	Suboptimal	Non adh	20 (58.8)	36 (55.4)	20 (40.8)	14 (25.5)	33 (28.2)
	Absent		6 (17.6)	4 (6.2)	2 (4.1)	5 (9.1)	4 (3.4)

NonAdh, nonadherents; Adh, adherents.

nonadherence and were judged adherent by the physician, while in 78 cases (24.4%) self-reported adherent patients were estimated to be nonadherent. Thus, a total of 111 physician-patient pairs (34.7%) were discordant. Using patient-assessed adherence as reference, sensitivity,

**Table 3. Unadjusted Association of Variables with Patient-Physician Discordance on HAART Adherence**

	OR (95% CI)
Patient-related variables	
Female gender	0.92 (0.55 to 1.53)
Age < 35 years	1.24 (0.78 to 1.97)
Injection drug use as HIV transmission mode	1.05 (0.65 to 1.69)
Education ≤ 8 years	2.03 (1.25 to 3.29)
Unemployment	2.01 (1.16 to 3.48)
Homelessness	3.19 (0.74 to 13.64)
Self-reported alcohol use	1.33 (0.68 to 2.59)
Self-reported intravenous drug use	1.14 (0.48 to 2.70)
Previous AIDS-related event	1.76 (1.01 to 3.07)
Poor mental health score (>1st quartile)	1.17 (0.47 to 2.92)
Perception of therapeutic efficacy of antiretrovirals	1.10 (0.69 to 1.76)
Dissatisfaction with care (<median score)	0.76 (0.46 to 1.23)
Perceived social support	0.86 (0.52 to 1.43)
Treatment-related variables	
No prior changes in ART regimen	0.85 (0.53 to 1.36)
Time on current HAART < 1 year	0.57 (0.30 to 1.08)
To run out of pills between clinic visits	1.27 (0.75 to 2.15)
To take complementary medicine	0.83 (0.37 to 1.90)
Clinic center-related variables	
To always be seen by the same physician	1.28 (0.80 to 2.03)
Absence of afternoon clinic hours	1.76 (1.07 to 2.91)
Absence of a psychologist	1.90 (1.01 to 3.59)
Absence of a social workers	2.05 (1.25 to 3.36)
Number of outpatients being seen > 500	1.02 (0.63 to 1.64)
Location in northern Italy	0.66 (0.38 to 1.15)
Academic medical center	0.61 (0.38 to 0.98)

OR, odds ratio; CI, confidence interval; ART, antiretrovirals; HAART, highly active antiretroviral therapy.

**Table 4. Variables Associated with Patient-Physician Discordance on Adherence; Multivariable Logistic Regression Analysis (Backward Stepwise Method)**

	OR (95% CI)
Patient-related variables	
Previous AIDS-related event	1.44 (0.77 to 2.69)
Unemployment	2.05 (1.12 to 3.74)
Education < 8 years	2.18 (1.30 to 3.66)
Clinic center-related variables	
Absence of afternoon clinic hours	1.78 (1.04 to 3.04)
Absence of a psychologist	0.78 (0.31 to 1.97)
Absence of a social worker	2.11 (1.22 to 3.63)
Academic medical center	1.14 (0.62 to 2.09)

OR, odds ratio; CI, confidence interval.

specificity, PPV, and NPV of physician-estimated adherence were 64.7%, 66.6%, 81.2%, and 45.8%, respectively. Kappa statistic was 0.27.

On bivariate analysis, factors related to discordance between patients and physicians included stage of HIV disease, being unemployed, less than 8 years of formal schooling, not having a psychologist or a social worker available in the clinical center, not having afternoon clinic hours, and being a nonacademic medical center (Table 3). None of the investigated symptoms was related to discordance. No difference was found between mean daily physician workload in concordant with respect to discordant cases ( $0.23 \pm 0.24$  vs.  $0.20 \pm 0.23$ ;  $P = .38$ ).

On multivariable analysis, less than 8 years of education (OR, 2.18; 95% CI, 1.30 to 3.66), unemployment (OR, 2.05; 95% CI, 1.12 to 3.74), absence of a social worker in the clinical center (OR, 2.11; 95% CI, 1.22 to 3.63), and unavailability of afternoon visits (OR, 1.78; 95% CI, 1.04 to 3.04) were significantly correlated with patient-physician discordance on adherence to antiretrovirals (Table 4).

## DISCUSSION

In this cohort of patients cared for in Italian ambulatory HIV specialty clinics, physicians did not correctly



estimate patient-reported adherence to antiretrovirals in more than one third of their HIV-infected patients. Patient-physician discordance about adherence to medications was more frequent for less educated people and those who were unemployed. Perhaps more important, concordance was also lower for people cared for in centers where social workers and afternoon office hours were not available.

Clinical prediction of patient attitudes and behaviors has been found wanting in almost every study in which it has been tested.<sup>19,20</sup> Poor predictive ability by physicians of their patients' status has been demonstrated for several health outcomes such as health-related quality of life,<sup>21</sup> symptoms,<sup>21-24</sup> functional disability<sup>25</sup> and performance status,<sup>26</sup> patient distress and perceived social support,<sup>27</sup> treatment goals,<sup>28</sup> quality of end-of-life communication,<sup>29,30</sup> and illicit drug use.<sup>31</sup>

In a study on the ability of primary care physicians to predict patient's adherence with digoxin therapy,<sup>14</sup> Gilbert et al. found that the sensitivity of clinical judgment for detecting nonadherence was 10% and overall performance by clinicians was not better than expected by chance. The predictive value of adherence was poor even for patients that physicians had known for 5 or more years. In previous studies on HIV-infected people, Paterson et al.<sup>4</sup> found that physicians miscategorized adherence for 41% of people; Haubrich et al.<sup>13</sup> found that the physician's estimate of adherence to antiretrovirals correlated with neither the patient self-assessment of adherence nor with virologic or immunologic outcomes. In HIV-infected homeless people, the rate of discordance on adherence between physicians and patients was similar to that in previously cited studies<sup>32</sup> while in a study on intravenous drug users, 60% of people self-reporting nonadherence were classified as adherent by their physician.<sup>33</sup>

In the present study, the rate of discordance (35%) between patients and physicians on adherence to drugs was substantial, though slightly better than previously reported in HIV-infected people when adherence was measured by electronic monitoring (41%)<sup>4,34</sup> or self-report (45%).<sup>13</sup> The rate of discordance in the present study was very similar to that of a study on adherence to treatment for diabetic adolescents<sup>35</sup> and the study on patients taking digoxin.<sup>4</sup> Physicians were more often discordant with patients when they rated them as adherent than when they rated them as nonadherent.

Poor concordance between patients and physicians is likely to lead to physician misclassification of a patient's adherence. Overestimation of nonadherence could lead to unnecessary use of resistance testing, and potentially unnecessary or harmful changes of therapy, including withholding or withdrawal of therapy. Nonadherent patients judged as adherent by their physician may receive drugs they do not take or that are useless, and unnecessary investigations for other potential reasons for therapeutic failure.

We found that lower patient education level, unemployment, absence of a social worker in the clinical center,

and visits not available also in the afternoons were significantly correlated to patient-physician discordance on adherence to antiretrovirals. To our knowledge, no previously published studies have found factors related to discordance between patient and physician with regard to medication adherence.

Several investigators have shown that unemployment is related to poor concordance between patients and physicians regarding several health outcomes.<sup>27,29,31,36</sup> One possible explanation for the effect of unemployment is that patients may have less in common with, and be understood less well, by the physician.

Lower educational attainment may influence concordance by a similar mechanism, or through different levels of language that may influence the patient-physician relationship. It is possible that discordance on adherence may be explained in part by inadequate communication between physician and patient.

Patients with HIV confront a number of social barriers to accessing service, and to maintaining their well-being. In the HIV Cost and Service Utilization Study (HCSUS), a large national probability sample of HIV-infected people, Katz et al.<sup>37</sup> demonstrated that the presence of a case manager was associated with fewer unmet needs and higher use of medications in patients receiving treatments. In this study, the availability of a social worker might offer patients additional means for their needs and expectations. They may help patients overcome fears about treatments, attend medical visits regularly, and help them interact with physicians about difficulties and concerns about therapy.

Greater accessibility of office hours was also associated with better concordance on adherence between patients and physicians, probably because it gives more opportunity to those more disadvantaged and with less flexibility with their schedules; moreover, it enhances interaction of the patient with the physician so that they can know each other better.

When physicians are unsure about patient adherence, or do not trust the patient's self-report, they are likely to rely on available clinical information.<sup>12,24,35</sup> This may explain why, in our study, physician-estimated optimal adherence was significantly correlated to undetectable levels of HIV RNA.

The present study conceals some limitations: first, the instruments we used in the present study need further validation processes. However, the patient's estimate of adherence was found to be effective in a previous study in capturing adherence to antiretrovirals when compared to the plasma pharmacokinetic levels of the same drugs.<sup>17</sup> Moreover, an indirect test of construct validity of the questionnaire was done by the significant association among patients self-reporting to be nonadherent and detectable HIV RNA.

Second, care should be taken in generalizing the finding regarding the variables influencing agreement between patients and physicians about adherence. It is likely that these might be population specific or related to organizational

aspects of each specific health care system. Third, we did not assess physician-related variables, such as age, gender, expertise and experience in treating people with HIV infection, workload, and academic charges.<sup>27</sup> It is possible that these variables could influence the relationship with patients and accuracy of clinical judgments about those patients. Moreover, we cannot be sure that physicians really did not have access to the HIV RNA and CD4 level values of the patient before answering the adherence questionnaire. Fourth, the patients' and the physicians' questionnaires differed in how the question about adherence was asked and their relative response options. This fact could have led to misclassification, although the dichotomization cutoffs were chosen to establish a strict definition of adherence to HAART.

Our findings suggest some strategies for improving physicians' assessments of their patients' adherence. First, efforts to improve communication could be triggered by evidence of discordance in physician versus patient assessments about the patients' health status or behavior. Ideally, this communication should be based on empathy, exhaustive information, and clarification about diagnosis, prognosis, and treatment,<sup>38</sup> confidence, and collaboration, in which patient feels listened to, respected, and expectations are met. In addition to improved communication, a parallel strategy would be the wider use of standardized adherence assessments,<sup>8</sup> such as self-reported questionnaires.<sup>2,17,39</sup> These standardized instruments may be especially useful when the physician considers initiating or changing an antiretroviral therapeutic regimen.

The second strategy would be to increase the use of a multidisciplinary team approach to care for HIV-infected people that is not limited to clinical problems and incorporates other health professionals such as social workers.

In conclusion, due to the crucial role of adherence for the effectiveness of treatment, the accurate identification of nonadherence should be of primary interest for physicians of HIV-infected people. The urgent task now is to improve the assessment of adherence and to enhance adherence. Because patients and physicians often are discordant on adherence to drugs, we suggest the regular use of a standardized self-reported adherence assessment method. Interventions to improve adherence should include strategies addressed to improve patient-physician communication. Improved communication, including patient lifestyle and preferences, can facilitate a frank exchange of information, negotiation, and a spirit of cooperation. More time should be spent assessing not only the best medication for a particular condition but also the best for a particular individual with a certain lifestyle and preferences. In this way, the complex process toward a real concordance between patient and physician will be accelerated. Further studies are needed to demonstrate that the use of this approach will improve the concordance between patient and physician and, eventually, patient outcomes.

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