

Long-Term Patient Adherence to Antiretroviral Therapy

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OBJECTIVE: To measure patient adherence to antiretroviral therapy over a two-year period and to identify factors impacting adherence.

METHODS: In a regional HIV treatment center, 100 consecutive patients starting any new antiretroviral agent were enrolled in this study, which consisted of a one-year retrospective data review and a one-year prospective component. The tools used for evaluating adherence were the monthly prescription refill data and a patient questionnaire. Data analyzed included overall adherence, adherence to individual antiretrovirals, and change in adherence over time, as well as factors reported as influencing adherence.

RESULTS: Greater than 80% adherence in taking prescribed doses was seen in 75% of patients during the retrospective phase of the study; adherence increased to 84% in the prospective phase. Throughout the prospective phase of the study, monthly median adherence rates were 98–100%. Suboptimal adherence secondary to pill fatigue or number of daily pills did not occur. Reported nonadherence to dietary restrictions varied among drugs. The primary cause given for poor adherence was difficulty remembering, followed by inconvenient dosing schedule and difficulty scheduling administration times around meals. At least one adherence tool was used by 61% of patients. A diagnosis of AIDS was associated with lower adherence in our patient population ($p = 0.039$); substance abuse and psychiatric history had no influence.

CONCLUSIONS: Adherence to antiretroviral treatment regimens did not diminish over the two years studied. Several patients with poor adherence were identified, emphasizing the importance of addressing this issue both prior to and throughout treatment. A personalized approach by healthcare providers can optimize patient adherence to antiretroviral therapy by providing careful drug selection in addition to routine follow-up and the provision of information, feedback, and reminder systems.

KEY WORDS: adherence, AIDS, antiretroviral therapy, compliance, HIV.

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Highly active antiretroviral therapy (HAART) has had a major impact on the course of HIV disease, producing a significant reduction in the incidence of both opportunistic infections and death.¹⁻⁵ However, it is becoming increasingly apparent that close adherence to the complex drug regimens comprising HAART plays a critical role in achieving complete viral suppression, which is essential for avoidance of drug resistance and treatment success.⁶⁻¹² Good adherence may require a patient to deal with difficult dosing regimens, food and storage restrictions, and a large pill burden, in addition to coping with possible adverse effects and lifestyle changes. This has led to the recommendation that careful preparation of therapy and follow-up are needed to enhance adherence.¹³ Trials of simpler maintenance therapies after response to initial HAART have so far not resulted in sustained viral suppression and cannot currently be recommended.^{14,15} The maintenance of good

adherence has been difficult in chronic illnesses¹⁶ and poses a particular challenge in HIV-positive patients, for whom suboptimal adherence rates have been documented.¹⁷⁻²⁴

Poor adherence may adversely affect three areas of clinical care: patient-specific outcomes, research outcomes, and the pharmacoeconomic justification of therapy. For individuals with HIV, cessation of antiretroviral treatment, and even brief periods of erratic adherence,²⁵ may result in rapid rebound of plasma viremia,^{13,26} selection of HIV strains resistant to drugs,^{13,27,28} and significant damage to the immune system.¹³ This not only compromises benefits of therapy, but may also pose a more general threat with possible selection and subsequent transmission of multidrug-resistant HIV.^{29,30} Clinicians must have accurate information on a patient's adherence to a regimen in order to assess treatment response³¹ and manage a therapeutic approach. Research is also affected by erratic adherence, which can decrease the reliability and validity of data that may be used to support interventions for other patients.³²⁻³⁴ Finally, noncompliance may have both direct and indirect cost im-

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plications.³⁵ The economic loss from poor adherence to antiretrovirals extends beyond the mere cost from the ineffective use of the drugs to the subsequent use of healthcare resources that would have been avoided if good adherence were maintained.³⁶

Many factors can affect adherence. Models of compliant behavior suggest an association between the patient's behavior and perceived susceptibility to and severity of illness.^{16,18,20,37} An individual's adherence may be adversely affected by lack of belief in the benefits of therapy,^{18,37,38} misunderstanding of the drug regimen and its importance,^{37,39} concern about confidentiality,³² intricate and complex dosage regimens,^{16,17,21} concurrent illnesses such as depression and psychological disturbance,^{12,19,20} adverse reactions,^{16,17,21,37,40} and therapy duration.^{16,17,21} Good adherence has been associated with supportive healthcare providers and a significant other, friend, or family member,^{16,20,32,35,39,41} use of reminder tools,^{18,42} and understanding of therapy.²²

The primary objective of this study was to measure patient adherence to antiretroviral therapy over a two-year period, with a one-year retrospective and one-year prospective component. Secondary objectives were to (1) assess differences in adherence with the use of individual antiretrovirals; (2) assess adherence to antiretrovirals in light of the total number of known medications; (3) quantify the use of compliance tools; and (4) determine the effect of other factors on adherence, particularly those identified by the patients, as well as substance abuse history, psychiatric history, and the diagnosis of AIDS. Substance abuse may have involved illicit drug and/or alcohol use. Psychiatric history was included if the patient was followed by a psychiatrist, regardless of medication control. We used a standard national definition for AIDS, in which a patient had an AIDS-defining illness regardless of CD4+ cell count.⁴³ These data may help target future efforts to improve adherence by providing enhanced care through interventions and focused counseling.

Methods

This descriptive study measured patient adherence over a one-year retrospective and a one-year prospective phase. One hundred patients attending the Southern Alberta HIV Clinic starting at least one new antiretroviral agent were recruited in a consecutive manner into a study approved by the University Conjoint Medical Ethics Committee. Patients received extensive pharmacy counseling and follow-up with this new antiretroviral initiation. The subjects were followed prospectively for 12 months (1997–1998). The retrospective part of the study involved data review on these patients for up to 12 months before recruitment into the prospective phase of the study.

Inclusion criteria were patients ≥ 18 years old and who were started on at least one new licensed antiretroviral medication at the time of enrollment. Exclusion criteria were patients not responsible for taking their own medications, including those in an institution or home where a care provider was accountable for drug administration; patients enrolled in antiretroviral research; and patients unable to complete a written questionnaire.

Patient adherence was measured by an objective prescription refill monitoring method in both the retrospective and prospective phases, and a subjective patient questionnaire method in the prospective phase. Refill information, particularly the number of days that patients were late in ob-

taining the medications, was retrieved from the dispensary computer system. Data were collected for all retrospective and prospective antiretroviral prescription refills to establish a continuous month-to-month adherence pattern for each patient. Since the HIV clinic provides sole access to antiretroviral drugs for patients in the region, including those hospitalized, the dispensary computer system was considered a reliable data source. The questionnaire, which was administered twice (6 and 12 mo after initial recruitment) gathered information on the number of times a patient varied from the prescribed regimen in the past seven days, reasons for nonadherence, and compliance tools used. Questions regarding variations from the prescribed regimen asked about doses missed or those taken incorrectly with regard to food. Patients were also asked to rank difficulties they experienced in taking the medications as prescribed. An option was given for the patients to provide written suggestions. The questionnaires were individualized to minimize confusion, listing the appropriate antiretroviral medications the patient was taking. The total number of oral medications, including antiretroviral drugs, was obtained through routine patient medication history and the chart, and was documented monthly if a drug was taken longer than 15 days. Medications prescribed on an as-needed basis, as well as multivitamins, herbs, or alternative medications, were not recorded.

A clinic pharmacist joined the healthcare team two months prior to study commencement. Thus, in the last two months of the retrospective phase and throughout the prospective phase of the study, the pharmacist performed standard practice services for all patients, including routine private interview; counseling and consulting sessions addressing adherence; monthly follow-up; pharmacotherapy monitoring; and interventions as required. The pharmacist was also available for additional consultations as requested by the patient or other healthcare team members or as determined by the pharmacist.

Data were shown as the percentage of patients demonstrating good adherence, using a then-standard definition of 80% adherence to the prescribed medications.^{9,18-20,22} A population of 100 subjects was selected so that if at least 50% of patients exhibited good ($>80\%$) adherence, then 100 patients would provide a 95% CI.

Percent adherence to licensed antiretrovirals was calculated for each calendar month. Month-to-month trends of medians and distributions of patient adherence were reported in a box-plot format, and the percentage of patients demonstrating $>80\%$ adherence was determined. Subanalysis, combining both retrospective and prospective data, involved box-plots depicting adherence to specific antiretrovirals and adherence to antiretroviral therapy based on total number of medications in the regimen. The influence of other possible factors on adherence was analyzed using the χ^2 method. All graphs and calculations were completed using StataQuest software (Stata Corporation, College Station, TX).

Adherence and compliance tool data from the questionnaires were expressed as means; barriers to adherence and suggestions were analyzed according to patient numbers and rankings.

Results

The first 100 eligible patients initiating or modifying antiretroviral therapy were recruited consecutively into the prospective phase of this study. One patient was appropriately recruited into the prospective study with an intention to treat; this patient was included to avoid bias in the analysis. Ninety-three subjects were men; ages ranged from 22 to 80 years old, with the largest group (30%) 31 to 35 years old. Twenty-one subjects had not completed high school, 30 had finished high school, 37 had received college or university education, and three had additional postgraduate training; no educational background information was available for eight subjects. CD4+ cell counts were >500 cells/mm³ (14 subjects), 200–500 cells/mm³ (38), 75–199 cells/mm³ (20), and <75 cells/mm³ (24); CD4+ cell counts for three subjects were not available. Viral load measures were <5000 copies/mL ($n = 19$), 5000–30 000 copies/mL (34), and >30 000 copies/mL (44); viral loads

for two patients were not performed prior to therapy initiation. The following comorbid diagnoses were present at the time of enrollment: 23 patients had AIDS, 21 patients received psychiatric care, and 25 had a history of substance abuse. Retrospective data were available for 63 subjects who had received previous antiretroviral agents.

Prescription refill data revealed good adherence (>80% of prescribed antiretroviral medication taken) in 75% of patients in the retrospective phase (n = 63) and in 84% in the prospective phase (n = 99). A month-to-month analysis (Figure 1) showed that the proportion of patients achieving >80% adherence was considerably higher starting in the last month of the retrospective phase of the study and throughout the prospective phase. Medians and distributions reflecting absolute antiretroviral adherence for the same patients on a monthly basis are shown using box plots in Figure 2. Due to the varying numbers of patients at these times, retrospective months eight through 12 are excluded. We found no seasonal variations in each patient's adherence rates.

Medians and box plot distributions of adherence to individual antiretrovirals, obtained from pharmacy refill data, are shown in Figure 3. Too few subjects were receiving zalcitabine to achieve meaningful analysis. Medians and

distributions with respect to total number of medications are shown in Figure 4; no statistical differences were detected for either. These analyses combined retrospective and prospective data.

Further analysis to address the effect on adherence was undertaken in patients with a history of substance abuse, those who had received previous psychiatric care, and those with a diagnosis of AIDS. No statistically significant differences were seen in patients with a history of substance abuse (median adherence 95%) or in the population with psychiatric disease (median adherence 98%). The number of patients taking >80% of prescribed medications did not significantly differ from the population without a history of substance abuse or psychiatric illness. Patients with AIDS had a median adherence of 95%. Seventy percent of patients with AIDS demonstrated >80% adherence compared with 88% of HIV-positive subjects without AIDS (p = 0.039).

Questionnaires were completed by 64 patients at least once. Fifty-one of 80 (64%) and 41 of 76 (54%) eligible patients (on licensed antiretroviral therapy that month) responded at six and 12 months, respectively. Those who did not respond failed to return the questionnaire(s) despite reminders or chose not to participate. Didanosine had the lowest reported adherence. The percentage of total doses that were reported to have been taken incorrectly with regard to dietary restrictions were reported as 3.6% (n = 5) for didanosine, 6.7% (n = 36) for indinavir, and 11.2% (n = 30) for saquinavir, where n is the number of patients who were taking the drug at the time the questionnaire was completed.

Sixty-one percent of the patients (n = 39) used at least one reminder device. Forty-eight percent of patients relied on a schedule as a tool, 20% used a dosette or pill box, 8% used an electronic reminder, and 4.7% employed watch alarms. Because patients selected their tools, analysis to see whether adherence was enhanced could be undertaken.

A number of additional suggestions were provided by 50 of the 64 patients who responded to the questionnaire(s). The majority emphasized the importance of linking medication administration with regular daily activities, for example, meals (n = 15, 23.4%), and of incorporating it into daily routine (n = 12, 18.8%). Some subjects listed the benefits of keeping medications visible (n = 4, 6.3%), carrying them (n = 3, 4.7%), and preparing them in advance in a dosette (n = 3, 4.7%). Other suggestions included taking medications in the same order each day to avoid confusion, having family or friends reminding them, using the ritonavir refrigeration pack, and following written menu suggestions. Subjects also ranked a number of difficulties experienced that may affect adherence (Table 1).

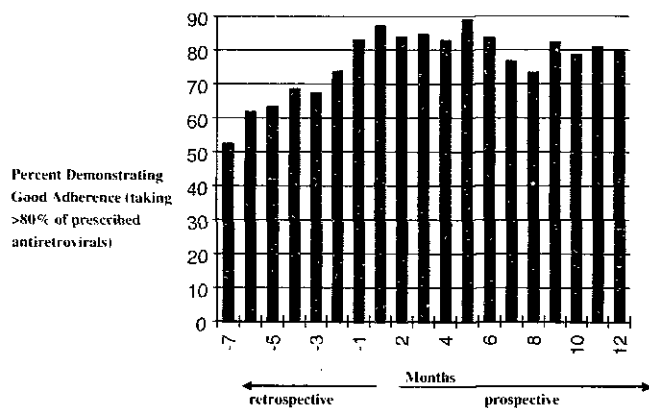


Figure 1. Monthly adherence.

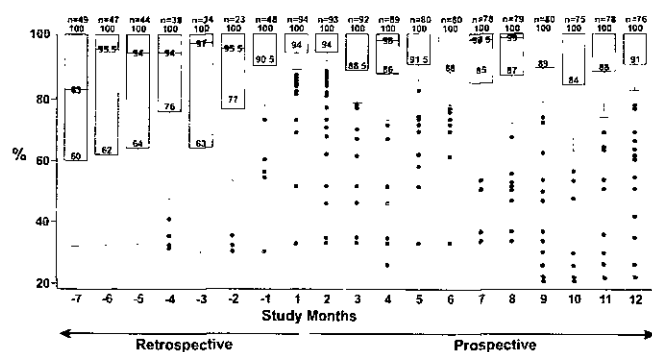


Figure 2. Monthly adherence (retrospective and prospective).

Discussion

Adherence to the antiretroviral medications in our population during this period was higher than that in previously reported trials.^{17,18,20,22} This may reflect different populations, different regimens, and different perceptions of the value of the treatment. Monthly median adherences of 98–100%, indicating half of the patients taking at least this fraction of the required dosages, were maintained throughout the prospective phase of the study. Eighty-four percent of patients demonstrated the >80% adherence benchmark. This definition is arbitrary; however, in the management of HIV disease a higher adherence rate may be necessary for maximal viral suppression and its associated positive health outcomes. Recent work¹² has suggested that >95% adherence is required in HIV management to achieve adequate clinical results.

The trend of adherence improving in the last months of the retrospective phase and remaining consistently higher throughout the prospective phase is an indication that ad-

herence can be sustained and even improved during lengthy courses of therapy. It also suggests that pill fatigue may not be an inevitable phenomenon. Several factors may have influenced this improved adherence. The wealth of information on the benefits of HAART became widely publicized at the time the adherence rate improved, potentially increasing belief in therapy, which has been shown to enhance adherence.^{18,37,38} Determination of viral loads (HIV RNA concentrations) also came into routine use in our clinic at that time, giving patients better insight into the rate of progression of their disease and regular reinforcement for their adherence. The treatment clinic relocated away from the hospital setting three months before this study began enrollment into the prospective phase, facilitating both access and care. A dedicated clinic pharmacist was also recruited to provide medication counseling, regimen scheduling, and interventions as required with routine follow-up. Positive impact resulting from pharmacists' consultations has been shown in several reports on the adherence rates of the HIV-positive^{9,10} and geriatric popula-

tions.⁴⁴ The ease of access and dedicated care provided have led to a more personalized approach to providing anti-HIV therapy, which may positively influence adherence. Despite these interventions designed to support adherence, subjects with suboptimal adherence were identified, which indicates a need for continued rigorous efforts to identify patients struggling to adhere to a regimen as well as a need to remove barriers to compliance.

Several medication regimen-related factors have been described as potentially impacting adherence. We could not identify any effect due to these factors from adverse effect profiles and storage requirements. Didanosine had the lowest self-reported adherence and a larger distribution of adherence rates. Adherence rates in our population were similar among individual protease inhibitors, as has been demonstrated elsewhere.¹² We did identify difficulties in complying with dietary restrictions. Pill burden was not a factor in predicting poor adherence. Our results support other work^{20,22} suggesting that dosing frequency may have a larger influence on adherence than the absolute number of medications. A limitation to our work, however, lies in combining retrospective and prospective adherence data for these two parameters.

We attempted to determine whether comorbid conditions impacted adherence. In our population, a history of having received psychiatric care had no significant impact on adherence; this finding was similar to that of Goetz and Rossman⁴⁵ and was in contrast to work of other groups.^{19,20} The literature also does not present a clear picture on whether a history of substance abuse adversely affects

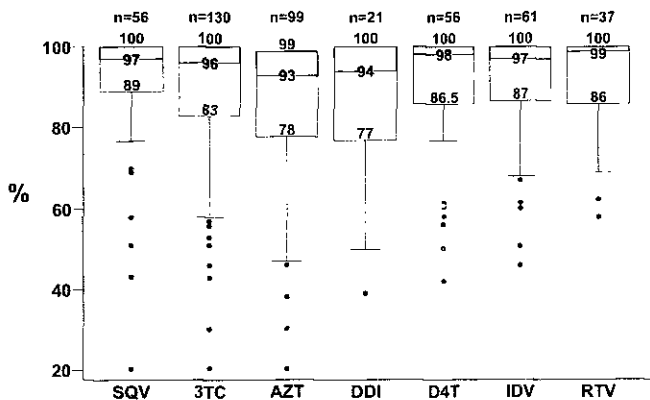


Figure 3. Adherence to individual antiretroviral agents. 3TC = lamivudine; AZT = zidovudine; D4T = stavudine; DDI = didanosine; IDV = indinavir; RTV = ritonavir; SQV = saquinavir.

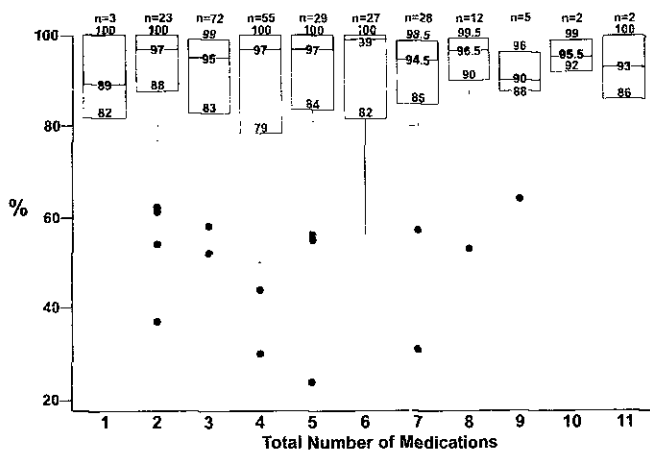


Figure 4. Adherence with respect to total number of medications.

adherence.^{12,18,19,20,45} The variations may also be explained by definitions, the individual populations studied, and concomitant barriers to adherence. In our study, fewer patients with a substance abuse history demonstrated good adherence; however, this was not statistically significant. A diagnosis of AIDS resulted in a significantly fewer number of patients taking >80% of prescribed antiretrovirals. This does not support models of compliant behavior that suggest increasing adherence with increasing severity of illness.^{18,20} Increasing pill burden associated with an AIDS diagnosis cannot be the cause, since it was not linked with adherence in this study.

The subjective data obtained from questionnaires showed that reported adherence rates were higher than those found by refill data. This is expected, since patient reports tend to overestimate adherence.^{12,16,46} Remembering to take doses was the most identified and highest-ranked difficulty; this is similar to data presented by other investigators.^{17,18,23,40} Nonadherence to dietary restrictions, a form of nonadherence other than missing a dose,⁴⁷ was also noted in our population and was most pronounced with saquinavir. Adverse effects were ranked fourth as a barrier to adherence. This is also in accordance with previous studies,^{17,21,48} where patients reported that difficulty remembering doses or inconvenient dosage regimens played a larger role than adverse reactions.

We used the information from prescriptions refilled and patient questionnaires to monitor adherence. Both represent indirect measures of adherence and have limitations, such as the absence of a guarantee of the drug being taken, but direct measures of adherence also have their drawbacks and were not feasible for this patient population. Blood concentrations or surrogate makers (e.g., elevations of mean corpuscular volume), for example, reflect only the most-recent medication-taking behavior.¹⁶ The use of microelectronic systems, although considered an innovative approach for monitoring adherence,⁴⁶ was not feasible for

our long-term study and, like indirect monitoring, does not guarantee a drug has been taken. Frick et al.⁴⁹ suggest that assessing adherence using pharmacy refill records may be equivalent to using electronic systems. To achieve a more accurate measure of compliance, it is recommended that two or more tools be used.¹⁶ We found the questionnaire most useful to obtain subjective data, to assess adherence to dietary restrictions, and to quantify the use of adherence tools. Perhaps the most practical approach for many pharmacists in clinical care is to use refill data adherence monitoring and to routinely invite discussion with the patient concerning doses missed or taken incorrectly and the reasons why. This may allow for a collaborative effort to remove any barriers to adherence and/or for the pharmacist to provide positive feedback and encouragement. One must also monitor for predicted antiviral effect and for signs of early virologic failure.

Summary

Optimizing adherence is clearly a critical path for managing routine care. Careful consideration of initial and subsequent therapy must include an individual evaluation of the potential for a patient to fully adhere to that treatment course.

Recognizing trends in adherence to therapy with anti-retroviral agents over time and the potential factors influencing adherence, this study further emphasizes the importance of healthcare providers' and, in particular, pharmacists' involvement. In addition to education on therapy with regular feedback, caregivers may improve adherence through individualization of patient-specific drug administration schedules, simplification of drug regimens, provision of reminder systems, simplification of access to anti-retrovirals, and dietary suggestions.

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Table 1. Barriers to Adherence Identified by Patients

Rank	Barrier	Score ^a
1	difficulty remembering morning dose	85
	afternoon dose	4
	evening dose	61
		26
2	inconvenient timing	76
3	difficulty scheduling around food	54
4	adverse effects	38
5	difficulty scheduling around sleep	22
6	size and number of medications	15
7	storage specifications	10
8	hydration requirements with indinavir	4
9	difficulty with discreet administration	3

^aScore was determined through a calculation considering both the frequency mentioned and the level ranked by subjects (frequency × rank 1 through 4); the higher the number, the more it is considered to be a barrier to adherence.

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enfaticó la importancia de atender este asunto antes y durante el tratamiento. Se enfaticó la atención personalizada en el cuidado médico y la seleccióncuidadosa de medicamentos para que las probabilidades de un buen cumplimiento fueran óptimas, al igual que el seguimiento de rutina y que se proveyera información, resultados de la terapia y sistemas que sirvan de recordatorio.

RAFAELA MENA DE GIRALDI

EXTRACTO

OBJETIVO: Medir el cumplimiento del paciente con la terapia antirretroviral durante un período de dos años e identificar factores que afectan el cumplimiento.

MÉTODOS: En un centro regional de tratamiento para el VIH se matricularon 100 pacientes que consecutivamente comenzaron tratamiento con algún agente antirretroviral nuevo. Este estudio consistió en una revisión de datos retrospectivos por un año y un componente prospectivo también de un año. Las herramientas utilizadas para evaluar el cumplimiento fueron los datos obtenidos de las repeticiones de prescripciones mensuales y un cuestionario dirigido al paciente. Los datos analizados incluyeron el cumplimiento total, el cumplimiento individual con los antirretrovirales, y los cambios en el cumplimiento durante el transcurso de tiempo, al igual que factores reportados que influyen el cumplimiento.

RESULTADOS: Se observó un cumplimiento mayor de 80% en la administración de las dosis prescritas en 75% de los pacientes durante la fase retrospectiva que aumentó a 84% en la fase prospectiva. Durante la fase prospectiva, las tasas media mensuales de cumplimiento fueron 98% a 100%. El cumplimiento subóptimo secundario al agobio que causa tomar un gran número de píldoras no ocurrió. La falta de cumplimiento con las restricciones dietarias reportada varió entre medicamentos. La causa principal para el cumplimiento pobre fue la dificultad para recordar, seguido de la inconveniencia del itinerario de dosificación y la dificultad de establecer un itinerario en torno a las comidas. Al menos una herramienta para medir cumplimiento fue utilizada por 61% de los pacientes. El diagnóstico de SIDA estuvo asociado con una disminución en el cumplimiento de los pacientes ($p = 0.039$), mientras que no influyó el historial de utilización de sustancias de abuso y de medicamentos para tratamiento psiquiátrico.

CONCLUSIONES: El cumplimiento con el régimen de tratamiento antirretroviral no disminuyó durante los dos años estudiados. Se identificaron varios pacientes que exhibían un cumplimiento pobre, y se

RÉSUMÉ

OBJECTIF: Mesurer l'observance à la thérapie antirétrovirale sur une période de deux ans et identifier les facteurs influençant la fidélité au traitement.

MÉTHODES: Dans un centre régional de traitement du HIV, 100 patients débutant un nouvel agent antirétroviral ont été inclus dans cette étude comportant deux phases, une phase rétrospective d'une durée d'un an et une phase prospective durant aussi un an. Les outils utilisés pour évaluer l'observance étaient le renouvellement mensuel de la prescription ainsi qu'un questionnaire administré au patient. L'observance globale, l'observance individuelle aux antirétroviraux, les changements de l'observance avec le temps ainsi que les facteurs influençant la fidélité au traitement étaient les données qui ont été analysées.

RÉSULTATS: Une observance de plus de 80% a été rapportée chez 75% des patients durant la phase rétrospective et chez 84% des patients durant la phase prospective. Durant la phase prospective, l'observance mensuelle variait entre 98% et 100%. Une observance sous-optimale secondaire à la corvée de prendre des médicaments ou à un nombre élevé de comprimés à prendre par jour n'a pas été observée. Certaines difficultés à respecter les restrictions alimentaires ont été identifiées avec quelques médicaments. La principale cause d'observance rapportée par les patients était l'oubli, suivi d'une posologie incommode et de la difficulté à planifier la prise des médicaments en fonction des repas. Au moins un outil pour favoriser l'observance était utilisé par 61% des patients. Un diagnostic de SIDA était associé à une moins bonne fidélité au traitement dans notre population ($p = 0.039$), alors que l'abus d'alcool ou l'utilisation de substances illicites et une histoire de trouble, psychiatrique n'influençaient pas l'observance au traitement.

CONCLUSIONS: L'observance à la thérapie antirétrovirale n'a pas diminué pendant les deux années étudiées. Plusieurs patients ayant une mauvaise observance à leur traitement ont été identifiés, soulignant ainsi l'importance d'encourager l'observance des patients tant au début de leur traitement que tout au long de celui-ci. Cette étude démontre qu'une approche personnalisée auprès de la clientèle HIV, la sélection des médicaments appropriés pour le patient, le suivi, la diffusion d'informations ainsi que la rétroaction sont autant de moyens d'optimiser la fidélité au traitement.

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