

## A 84-month follow up of adherence to HAART in a cohort of adult Senegalese patients

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### Summary

**OBJECTIVES** To assess long-term adherence of the first HIV-1 patients receiving highly active antiretroviral therapy (HAART) in Senegal, and to identify the main determinants of adherence.

**METHODS** The first 180 patients enrolled in the Senegalese HAART initiative between August 1998 and April 2001 followed up for at least 30 days were eligible. Adherence was assessed monthly at each drug dispensation between November 1999 and November 2006 by a pharmacist using a pill count completed by a questionnaire. Adherence was expressed as the proportion of tablets taken to prescribed tablets. An adherence of 95% was considered to be good. A random-intercept logit model was fitted to identify the main determinants of adherence.

**RESULTS** Adherence data were available for 158 of 167 eligible patients. Twenty-nine patients died during the study period and 10 were lost to follow-up. Median treatment duration was 78 months, accruing to 6657 person-months of observation. Overall, mean adherence reached 91% [median: 100%, interquartile range (IQR) 96-100%] and adherence exceeded 95% in 78% [95% CI 77-79%] of observations. After 4 years of treatment mean adherence stabilized around 90% and adherence  $\geq 95\%$  stabilized around 70%. Treatment duration and protease inhibitor (PI)-based regimen (indinavir) had a negative effect on adherence, but adherence tended to improve with time for patients receiving a PI. Patient-level variance was highly significant and accounted for a third of total variance.

**CONCLUSIONS** This work demonstrates that good long-term adherence can be achieved in the sub-Saharan context given close monitoring and adherence support measures, confirms the worse adherence for indinavir and underlines the importance of patient heterogeneity.

**keywords** patient compliance, human immunodeficiency virus, highly active antiretroviral therapy, Senegal

### Introduction

Adherence is defined as a measure of the difference between a physician's prescription and a patient's behaviour. Review of the literature shows that the overall rate of non-adherence could reach 50% in chronic treatment regimens such as tuberculosis or antiretroviral treatment (ART) in HIV patients (Christensen 2004). This may be the single most important challenge faced by healthcare

providers today and, in cases where HIV-infected patients receive highly active antiretroviral therapy (HAART), it may lead to virus mutation and drug resistance. A long-term high level of adherence is usually recommended to delay disease progression, to achieve lasting viral suppression and to avoid drug resistance (Paterson *et al.* 2000, Bangsberg *et al.* 2001, WHO 2003). Assessment of adherence is however extremely difficult because it is mainly a behavioural process. It varies over time, no gold standards exist and, consequently, we lack valid measurement tools (Bangsberg *et al.* 2001; Costagliola &

\*See Appendix for the participants of the Study Group.

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Barberousse 2001, Spire 2003). In the specific case of HIV/AIDS, a whole range of measurement tools of non-adherence have been tested and used: regularity to scheduled visits, self-reports (diaries, questionnaire), physician's appraisals, face-to-face questionnaires, direct observation of patients, pill counts, plasmatic drug dosage, biological markers and electronic monitoring devices (Spire 2003). In sub-Saharan African countries, documenting the long-term pattern of adherence to HAART is of paramount importance with respect to scaling-up initiatives and to the persistent debate of adherence ability among African patients on HAART (Müller *et al.* 1998; Gill *et al.* 2005; Attaran 2007).

In November 1999, we started a pilot project designed to assess adherence and causes of treatment interruption among patients treated through the Senegalese Antiretroviral Access Initiative (ISAARV) (Desclaux *et al.* 2004). Quantitative descriptive and analytical results up to 3 years after HAART initiation have already been published (Desclaux *et al.* 2003; Lanièce *et al.* 2003). We report here on long-term trends in adherence and determinants.

## Patients and methods

### Study design

Details of the study population, inclusion and exclusion criteria have previously been published (Lanièce *et al.* 2003). Briefly, the first 180 HIV-1 infected adults enrolled in the ISAARV between August 1998 and April 2001 and monitored medically for at least 30 days were eligible for the study. Clinical and biological follow-up visits followed the routine procedure of the ISAARV and were described in detail elsewhere (Lanièce *et al.* 2003; Etard *et al.* 2006). After pre-enrolment and enrolment visits, patients were examined at week 2, month 1 and month 2, after HAART initiation and then at least every 2 months. CDC stage classification was used (CDC 1992). Immunovirologic evaluations were carried out every 6 months. CD4 counts were assessed using the FACSCount System (Becton Dickinson) and plasma viral load using either the Amplicor HIV-1 1.5 or 2.0 assay (Roche Molecular Systems) or the Bayer bDNA HIV-1 Quantiplex assay 2.0 or 3.0 (Bayer Diagnostics). All these tests were performed in Dakar.

### Adherence

Desclaux *et al.* (2003) described adherence support measures. First, counselling on technical matters such as regimen or adverse events was provided by the physician or the pharmacist. Secondly, information was also channelled

through discussion groups which were set up at one prescription site. Thirdly, every month, research assistants, a pharmacist, an anthropologist, social workers and members of people living with AIDS associations met to track patients who had not shown up for scheduled visits. Telephone calls were placed and home visits were organized to identify deaths or to discuss reasons for non-adherence. These discussions helped to resume treatment among several missing patients. Confidentiality regarding HIV status was strictly observed during all contacts.

Adherence assessment started in November 1999. Fifty-nine patients were already on HAART at that date. Adherence data were therefore missing for these patients between their date of HAART initiation and their first adherence assessment. For the remaining 99 patients, adherence assessment started with their first month on HAART.

All the patients obtained their drugs from a pharmacist at a single dispensing site (Fann Hospital). Between August 1998 and December 2003, patients enrolled in the ISAARV partially contributed to the cost of their treatment every month if they were not included in a clinical trial. The amount paid depended on income, but treatment could be entirely subsidized if the patients' income was considered too low by the Welfare and the Eligibility Committees (Desclaux *et al.* 2004). A sharp decrease in drug prices took place in November 2000 and ART became free for all patients beginning in December 2003 (Desclaux *et al.* 2004). The amount paid by the patient was recorded by the pharmacist at each drug dispensation. ART regimen was a triple-drug combination [2 NRTIs (nucleoside reverse transcriptase inhibitor) + 1 NNRTI (non-nucleoside reverse transcriptase inhibitor) or 1 protease inhibitor (PI)]. The dispensing procedures and support measures were the same for all the patients.

The pharmacist assessed adherence at each drug dispensation (starting from the first day) using a structured questionnaire collecting information on dates of prescriptions, reasons for any delays, patients' understanding of prescriptions, any reasons for non-adherence and a count of returned pills. Questions were asked in the local language or in French. Three pharmacists were sequentially involved throughout the study. Adherence was expressed as the mean of the proportion of tablets taken to prescribed tablets for each antiretroviral drug during the past 30 days:

$$\text{Adherence for patient}_i \text{ for month}_j \\ = \frac{\sum_{k=1}^3 \text{taken}_k / \text{prescribed}_k}{3}$$

In case of early visits, the pharmacist gave a new appointment to count the pills over a 30-day period. In

case of late visits, the reference period remained the last 30 days and therefore the adherence could not be 100%. Some missing information because of irregular visits to the pharmacy was subsequently obtained by the physician or the social worker in contact with the patient.

### Statistical analysis

Data were censored at 84 months from HAART initiation as of 30 November 2006. A running-mean smoothing was applied to the monthly adherence to ease the graphical appraisal of the long-term trend. Baseline factors included age at HAART initiation, gender and CDC stage. Patient's financial participation, PI-based regimen and time elapsed since HAART initiation were time-dependent. Financial participation became null for all patients as of December 2003. A logit mixed model for repeated measures with a random intercept and a random coefficient on time, starting with main effects and first-order interactions, was fitted. Factors were included in an initial model based on a threshold  $P$ -value  $\leq 0.35$ . The relationship between adherence and virologic efficacy was explored 6 months after HAART initiation among a sub-sample of naive patients whose 6-month viral load was available. STATA 9 and R softwares were used.

### Ethical considerations

Ethical approval was received from the Committee of the AIDS Control National Program. Patients with poor adherence were referred to the Welfare Committee and were offered appropriate support.

### Results

A total of 167 patients were eligible, three were excluded for refusing to participate and adherence data were missing for six patients. Therefore analysis was performed on 158 patients [M:F ratio = 1:1 (79:79), mean/median age = 38 years, clinical CDC stage B = 37% (59/158) and C = 58% (92/158), median viral load =  $5.3 \log_{10}$  cp/ml, median CD4-cell count =  $136/\text{mm}^3$ , ART-naive = 95% (149/158)]. Median monthly income at inclusion was 23€. Initial ART regimen was a triple-drug combination [2 NRTIs (didanosine, stavudine, zidovudine, lamivudine) + 1 NNRTI (efavirenz) or 1 PI (indinavir)]. The three main regimens were: didanosine/stavudine/indinavir (44/158), didanosine/lamivudine/efavirenz (40/158) and didanosine/stavudine/efavirenz (39/158). Indinavir-based regimen accounted for 42% of the initial regimen. Later, nelfinavir was prescribed but remained marginal compared with indinavir.

Adherence follow-up until 30 November 2006 and up to 84 months after HAART initiation yielded 6657 person-months of observation. Median number of measurements per patient reached 47 (IQR 38–53). Median treatment duration was 78 months (IQR 68–82). Twenty-nine deaths occurred during the study period and 10 patients were lost to follow-up (after 6 months without any news).

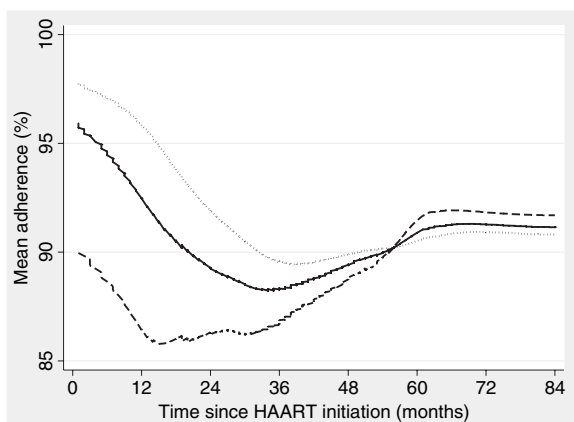
In November 1999, at the beginning of the study, patients paid on average 22 180 FCFA (34€) per month (range: 0–75 000, median = 21200), and 81% of them paid more than 10 000 CFA (15€). One year later, the cost was halved (11 100 CFA and 44%). In November 2001, these figures dropped to 2900 CFA and 7% and in December 2003, 4 years after the study began and just before treatment was completely free, to 633 CFA and 1.4%.

In the sub-sample of 80 naive patients whose 6-month viral load was available, 72% of the patients with a mean adherence over the first 6 months of treatment above 90% presented an undetectable viral load while all the patients with an adherence below 90% had a detectable viral load (Fisher exact test,  $P = 0.08$ ). Mean monthly adherence decreased until the fourth year before stabilizing around 90% while at least half of the monthly adherence measurements were equal to 100%. Good adherence ( $\geq 95\%$ ) followed the same pattern and stabilized slightly above 70% (Table 1). After smoothing monthly data, the same trend was observed with a plateau for the most recent months (Figure 1).

Univariate results are presented in Table 2. Good adherence decreased with time after HAART initiation with both significant linear and quadratic trends. A PI-containing regimen was associated with worse adherence. Multivariate analysis retained a decreasing linear trend and an increasing quadratic trend in adherence with treatment duration, suggesting a better outcome for the last months. The PI-containing regimen effect is shown but the interaction term, time  $\times$  PI, is significant: while over the whole follow-up adherence was worse for patients receiving a PI, it tended to improve with time (Table 3). This interaction can be seen in Figure 1. A sub-group analysis comparing the two PI used, indinavir and nelfinavir, to a non-PI-containing regimen showed that indinavir was responsible for the effect. The random effect on the intercept was significant ( $P < 10^{-4}$ ) and the ratio of the patient-level variance to the total variance ( $\rho$ ) reached 30%, indicating a large heterogeneity between patients. A random effect on time coefficient was not necessary.

**Table 1** Mean and median adherence and adherence above 95% aggregated by year on HAART, Senegal, 1998–2006 ( $n = 158$ , 6657 person-months)

Year since HAART initiation	No. patients on treatment	No. measures (person-months)	Mean adherence [95% CI]	Median adherence [IQR]	Adherence $\geq 95\%$ (%) [95% CI]
1	141	1232	95.5 [94.6–96.4]	100 [100–100]	87.0 [85.0–88.8]
2	145	1400	89.7 [88.3–91.1]	100 [96–100]	78.8 [76.6–80.9]
3	135	1105	88.5 [86.8–90.2]	100 [96–100]	78.2 [75.6–80.5]
4	133	955	87.4 [85.6–89.3]	100 [93–100]	74.2 [71.3–76.9]
5	126	794	91.5 [90.0–92.9]	100 [93–100]	72.8 [69.5–75.8]
6	123	738	91.5 [89.9–93.0]	100 [93–100]	71.9 [68.5–75.1]
7	89	433	91.2 [89.2–93.2]	100 [93–100]	73.4 [69.0–77.5]

**Figure 1** Mean adherence since HAART initiation, ISAARV cohort, Senegal, 1998–2006 (running-mean smoothing). Overall trend (—), PI-containing regimen (- - -), non PI-containing regimen (. . .).**Table 2** Univariate logistic regression analysis of an adherence above 95%, Senegal, 1998–2006 ( $n = 158$ , 6657 observations)

Variable	OR	95% CI
Age at baseline $\geq 38$ years	1.10	0.75–1.60
Sex (M vs F)	1.11	0.77–1.61
CDC stage at baseline (B/C vs A)	0.35	0.16–0.78*
Time since HAART initiation (year)	0.81	0.79–0.84**
Time since HAART initiation squared (year)	0.97	0.96–0.98**
Monthly financial participation >15 euros	1.06	0.86–1.35
PI in the treatment	0.89	0.70–1.13

\*Wald test:  $0.01 < P < 0.05$ .\*\*Wald test:  $P < 0.001$ .

## Discussion

### Methods

Various methods have been proposed to measure adherence, from frequency of attended appointments or self-report instruments to plasmatic dosage or electronic monitoring devices. The use of two methods, one relying on patients' report, is recommended (Costagliola & Barberousse 2001). Even the most sophisticated tool, the electronic device, cannot be considered as a gold standard (Costagliola & Barberousse 2001; Bova *et al.* 2005). We used two assessment tools: a face-to-face structured questionnaire completed by the pharmacist and a pill count, considered as an intermediate tool in the hierarchy of accuracy of adherence measures (Gill *et al.* 2005). These means are cheap, easy to implement and complementary in the sense that the patients' answers are checked against pill counts, limiting overestimation. In the same manner that self-reports and other measures have been shown to correlate with viral outcomes (Costagliola & Barberousse 2001; Oyugi *et al.* 2004; Nieuwkerk & Oort 2005), we verified the correlation between assessed adherence and virological success during the first 6 months of treatment to validate our tool. Such validation was performed in our previous report using a slightly different methodology (Lanièce *et al.* 2003).

In 2004, HIV prevalence in sentinel pregnant women in Senegal reached 1.7% (range: 0.3–3.6%), with spatial heterogeneity between south and north and urban–rural areas, and the highest prevalence being observed in Dakar and Ziguinchor (République du Sénégal 2006). The number of adult HIV-infected patients is not precisely known: the Ministry of Health provided an estimate of 77 000 in 2000 (République du Sénégal 2001) while projections using EPP and SEPCTRUM spreadsheets based on 2004 sentinel surveillance data yielded 46 000 prevalent infections (République du Sénégal 2006, UNAIDS 2007). The

**Table 3** Logit mixed-effects model of an adherence above 95%, Senegal, 1998–2006 ( $n = 158, 6651$  observations)

Variable	All PI OR [95% CI]	IDV-based OR [95% CI]	NFV-based OR [95% CI]
Time since HAART initiation (year)	0.53 [0.46–0.62]*	0.52 [0.45–0.61]*	0.52 [0.43–0.62]*
Time since HAART initiation, squared (year)	1.04 [1.02–1.06]*	1.05 [1.03–1.07]*	1.05 [1.02–1.08]*
PI in the treatment	0.32 [0.22–0.46]*	0.29 [0.20–0.42]*	0.95 [0.30–3.07] ns
Time by PI	1.29 [1.20–1.40]*	1.30 [1.20–1.41]*	1.14 [0.87–1.49] ns
Random effect (SD)	1.15 [0.99–1.32]*	1.15 [0.99–1.33]*	1.14 [0.95–1.36]*
	rho: 0.29	rho: 0.29	rho: 0.29

\* $p < 0.001$ .

UNAIDS estimates the range of infections between 26 000 and 92 000 (UNAIDS 2006). Since its initiation in August 1998, the Senegalese programme has evolved and the number of patients on HAART, as of March 2006, was estimated around 4000 patients, covering 35% of patients in need of ART (WHO 2006). Therefore, the 180 HIV-1 eligible adult patients of our study represent only a small fraction of the patients put on HAART in Senegal. They cannot be compared with the current cohort of patients enrolled in the ISAARV for several reasons: the baseline characteristics of the patients included in the ISAARV are likely to have changed with time, treatment has become free for all new patients from the first month, current first-line regimen has evolved and excludes PI, the group of 180 patients were closely monitored because they were the first to receive ART and the cost of their follow-up was entirely covered by the research grants. Therefore, we cannot generalize our results to the current patients on HAART in Senegal. However, this study provides the only long-term quantitative adherence assessment in this country.

## Results

This updated analysis confirmed the high level of adherence attained up to 7 years after HAART initiation: mean adherence around 90% and adherence  $\geq 95\%$  exceeded 70% beyond the fourth year of treatment. These estimates are in keeping with the recent meta-analysis (including 27 sub-Saharan studies and 12 116 patients) which yielded a pooled estimate of 77% (95%CI 68–85%) (Mills *et al.* 2006). In a cross-sectional study in Malawi, Médecins sans Frontières reports a similar estimate of self-reported adherence in the past 4 days (Ferradini *et al.* 2006). Taken together, these studies convey the growing evidence that high level of adherence to complex therapies can be achieved in low-income countries, given strong support measures. Our report suggests in addition that a high level can also be maintained in the long term (7 years).

In our previous analysis on determinants of adherence between November 1999 and November 2001, financial participation was associated with poor adherence (Lanièce *et al.* 2003). The same barrier was indeed observed elsewhere in sub-Saharan Africa (Weiser *et al.* 2003, Orrell 2005). Patients' financial participation dropped sharply in November 2000 thanks to a government agreement with pharmaceutical firms and it kept decreasing until December 2003 when it became null. This pattern explains why the effect of the financial participation, initially shown on a short follow-up until November 2001, was not observed over a 7-year follow-up. A financial participation effect could not be estimated after December 2003 as financial participation was null.

Advanced HIV stage is inconsistently associated with adherence (Spire *et al.* 2001; Orrell *et al.* 2003). A non-differential misclassification bias because of the inaccuracy of the measure could indeed hide this effect. In our study, CDC stage B/C at baseline was no longer a risk factor of low adherence at the multivariate stage. However, in this repeated-measure design, HIV stage at baseline does not reflect the status of patients at a later time and, in addition, patients cannot move down in the classification.

In our first report, we pointed out a lesser adherence for patients receiving a PI, such as indinavir, compared with patients receiving a NNRTI, such as efavirenz (Lanièce *et al.* 2003). This PI effect is still present in the long term, as is reported in developed countries (Salmon-Ceron *et al.* 2000; Maggiolo *et al.* 2005; Rubio *et al.* 2005; Carrieri *et al.* 2006). Apart from side effects, this effect is probably due to recommendations to take PI tablets in accordance to the timing of the meal with sufficient hydration.

We showed that the patients included in this research cohort were able to maintain a good adherence for a long term, given a close follow-up and active support adherence interventions. Good and long-term adherence in a scaling-up perspective remains to be demonstrated in Senegal.

However, recent reports from Uganda showed that good adherence can be achieved by a programme delivering home-based care in a low-income rural setting and that reasons for non-adherence are more structural than behavioural (Crane *et al.* 2006; Weidle *et al.* 2006). Patients' financial participation is no longer a barrier to HAART access in Senegal because treatment is now free. The nature of the regimen should receive attention, and current WHO recommendations for first-line treatment, excluding unboosted PI, should be followed. Our analysis also pointed out a large heterogeneity between patients, which argues in favour of patient-tailored support measures. Finally, we agree that there is still a need to continue to validate drug adherence measures (Kerr *et al.* 2005; Crane *et al.* 2006).

### Acknowledgements

We would like to sincerely thank the social workers and members of PLWA associations for their input in helping patients with their treatment. The authors are grateful to Dr Bernard Taverne for his advice in conducting this study and careful review of the manuscript.

### Appendix – ANRS 1215/1290 Study Group

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J.-F. Etard *et al.* **Seven-year follow-up of HAART in Senegal****Suivi de l'observance au traitement antirétroviral sur une période de 84 mois dans une cohorte de patients adultes au Sénégal**

**OBJECTIFS** Evaluer l'observance à long terme des premiers patients infectés par le VIH-1 recevant une multithérapie antirétrovirale au Sénégal et identifier les principaux déterminants de l'observance.

**MÉTHODES** Les 180 premiers patients inclus dans l'Initiative sénégalaise d'accès aux médicaments antirétroviraux entre août 1998 et avril 2002, suivis pendant au moins 30 jours, étaient éligibles. L'observance a été évaluée mensuellement à chaque fourniture de médicaments entre novembre 1999 et novembre 2006 par un pharmacien réalisant un décompte des comprimés complété par un questionnaire. L'observance a été exprimée comme la proportion de comprimés pris sur prescrits. Une observance de 95% a été considérée comme bonne. Un modèle logistique à intercept aléatoire a été ajusté pour identifier les principaux déterminants de l'observance.

**RÉSULTATS** Les données d'observance étaient disponibles pour 158 des 167 patients éligibles. Vingt-neuf patients sont décédés pendant la période d'étude et 10 ont été perdus de vue. La durée médiane de traitement était de 78 mois cumulant 6657 personnes-mois d'observation. L'observance globale moyenne atteignait 91% [médiane : 100%, IIQ : 96-100%] et l'observance dépassait 95% dans 78% [IC95% : 77-79] des observations. Après 4 ans de traitement, l'observance moyenne et l'observance  $\geq 95\%$  se stabilisaient, respectivement, autour de 90% et de 70%. La durée de traitement et un régime comprenant un inhibiteur de protéase (indinavir) étaient globalement associés à une observance moins bonne mais celle-ci avait tendance à s'améliorer au cours des mois les plus récents chez les patients recevant un inhibiteur de protéase. La variance inter-patients était hautement significative et expliquait un tiers de la variance totale.

**CONCLUSIONS** Ce travail démontre qu'une bonne observance à long terme peut être obtenue dans un contexte sub-saharien grâce à un suivi rigoureux des patients et des mesures d'accompagnement, confirme une observance moins bonne à l'indinavir et souligne l'importance de l'hétérogénéité des patients.

**mots clés** compliance du patient, VIH, traitement antirétroviral, hautement actif, Sénégal

**Seguimiento de 84 meses de la adherencia a la Terapia Antirretroviral Altamente Activa en una cohorte de pacientes senegaleses adultos**

**OBJETIVOS** Evaluar la adherencia a largo plazo de los primeros pacientes con VIH-1 recibiendo Terapia Antirretroviral Altamente Activa (HAART) en Senegal, e identificar los principales determinantes para la adherencia.

**MÉTODOS** Los primeros 180 pacientes incluidos en la iniciativa senegalesa de HAART entre Agosto 1998 y Abril 2001, y seguidos durante al menos 30 días, fueron aptos. La adherencia se evaluó de forma mensual, por un farmacéutico que utilizaba un contador de pastillas y completaba un cuestionario. Se realizó en todos y cada uno de los lugares que dispensaban tratamiento, entre Noviembre 1999 y Noviembre 2006. La adherencia fue expresada como la proporción de pastillas tomadas sobre el número de pastillas prescritas. Se consideró una adherencia del 95% como buena. Se utilizó el modelo de interceptos aleatorios de logit con el fin de identificar los principales determinantes de la adherencia.

**RESULTADOS** Se obtuvieron datos de adherencia para 158 de 167 pacientes aptos. 29 pacientes murieron durante el periodo del estudio y 10 se perdieron durante el seguimiento. La duración media del tratamiento fue de 78 meses, acumulándose 6657 personas-mes de observación. En total, la adherencia media alcanzó un 91% [mediana: 100%, IQR 96-100%] y la adherencia superó el 75% en un 78% de las observaciones [95% CI 77-79%]. Después de 4 años de tratamiento, la adherencia se estabilizó alrededor del 90% y la adherencia de  $>95\%$  se estabilizó alrededor del 70%. La duración del tratamiento así como el régimen basado en indinavir IP tenían un efecto negativo sobre la adherencia, pero la adherencia tendía a mejorar con el tiempo en pacientes que recibían un inhibidor de la proteasa. La varianza del nivel del paciente era altamente significativa y la responsable de una tercera parte del total de la varianza.

**CONCLUSIONES** Este trabajo demuestra que se puede alcanzar una buena adherencia a largo plazo dentro del contexto de África Sub-Sahariana si se toman unas medidas de apoyo a la adherencia adecuadas así como de monitorización; confirma también una peor adherencia para indinavir y subraya la importancia de la heterogeneidad de los pacientes.

**palabras clave** cumplimiento pacientes, VIH, terapia antirretroviral, altamente activa, Senegal