Revisiting Long-Term Adherence to Highly Active Antiretroviral Therapy in Senegal Using Latent Class Analysis

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Background: Adherence is one of the main predictors of antiretroviral treatment success. A governmental initiative was launched in 1998 for HIV-infected patients in Senegal to provide access to highly active antiretroviral therapy.

Methods: Between August 1998 and April 2002, 404 adult patients were enrolled. Adherence measurements, defined as pills taken/pills prescribed, were assessed between November 1999 and April 2009 using a pill count along with a questionnaire for 330 patients. Predictors of adherence were explored through a random-intercept Tobit model and a latent class analysis (LCA) was performed to identify adherence trajectories. We also performed a survival analysis taking into account gender and latent adherence classes.

Results: Median treatment duration was 91 months (interquartile range, 84–101). On average, adherence declined by 7% every year, was 30% lower for patients taking indinavir, and 12% higher for those receiving cotrimoxazole prophylaxis. Based on the predicted probability of having an adherence ≥ 95%, LCA revealed 3 adherence behaviors and a better adherence for women. A quarter of patients had a high adherence trajectory over time and half had an intermediate one. Male gender and low adherence behavior over time were independently associated with a higher mortality rate.

Conclusions: This study shows that an overall good adherence can be obtained in the long term in Senegal. LCA suggests a better adherence for women and points out a large subsample of patients with intermediate level of adherence behavior who are at risk for developing resistance to antiretroviral drugs. This study warrants further research into gender issues.

Key Words: antiretroviral therapy, adherence, latent class analysis, mixed model, women, Senegal

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INTRODUCTION

Highly active antiretroviral therapy (HAART) was introduced in 1996, leading to a decrease in HIV-related death rate, and well documented in high-income countries.[1] Although access to antiretroviral drugs expanded greatly over the past 5 years in sub-Saharan Africa, program coverage is still below 50%. Poor coverage results from testing policies, treatment costs, patients' resources, shortage in trained health care workers, and international structural constraints.[2–7]

Although antiretroviral therapy has resulted in dramatic reductions in mortality and morbidity in HIV infection, adherence to drugs greatly influences treatment success.[8] Adherence, defined as the process in which patients follow health care provider recommended treatment with optimal regularity, and after CD4 cell count, is an indisputable indicator of progression to AIDS.[8,9] According to published studies, nonadherence to antiretroviral treatment in HIV-infected adult patients ranges between 33% and 88% while an adherence above 95% is required to achieve full and continuous viral suppression.[8–12] However, in the absence of a gold standard, adherence is very difficult to assess accurately. Many factors related to patient behavior, treatment, and time affect adherence, so assessment tools need to be appropriated.[13–15]

In 1998, a pilot project, the Senegalese drug access initiative (ISAARV), was launched and Senegal became one of the first sub-Saharan African countries to establish a public distribution program.[16] In November 1999, a little more than 1 year after the launch of the program, a therapeutic follow-up project began with the aim of assessing adherence and determining causes of nonadherence. Three years and 7 years after HAART initiation, 2 analyses of adherence have already been published.[17,18] Here, we report on the principal determinants of adherence up to 9 years after HAART

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initiation. We also provide a new approach to analyze adherence and point out differences between patients' behaviors to guide policies to improve adherence.

METHODS

Study Design

A total of 404 HIV-1–infected adult patients were enrolled in ISAARV in Dakar and in an observational cohort between August 1998 and April 2002. The first 180 patients were enrolled between August 1998 and April 2001, and 80 of these participated in 2 clinical trials according to the following inclusion criteria: (1) being antiretroviral therapy naive, (2) having a CD4 cell count $<$ 350 cells per microliter, (3) a plasma viral load $>$ 30,000 copies per milliliter, and (4) a Karnofsky score $\geq$ 70%. The remaining 100 patients and the other 224 included in ISAARV until April 2002 were enrolled if they met one of the following criteria: (1) for asymptomatic patients: CD4 cell count $<$ 350 cells per microliter and plasma viral load $>$ 10^5 copies per milliliter and, from October 2000, CD4 cell count $<$ 200 cells per microliter; (2) for paucisymptomatic patients: CD4 cell count $<$ 350 cells per microliter and plasma viral load $>$ 10^4 copies per milliliter and, from October 2000, CD4 cell count $<$ 200 cells per microliter; and (3) for symptomatic patients: Karnofsky score $>$ 70%, regardless of CD4 cell count and plasma viral load, and without active major opportunistic infections. After preenrollment and enrollment visits, patients were followed up at week 2, month 1, and month 2 after HAART initiation and then at least every 2 months. They received a cotrimoxazole prophylaxis when their CD4 cell count was $\leq$ 350 cells per microliter. Every 6 months, biological evaluations, including CD4 cell count and HIV plasma viral load, were performed in Dakar. Laboratory procedures are described in a previous report.[19] CDC (Centers for Disease Control and Prevention) stage classification (1993 revision) was used.

Adherence Measurements

Adherence assessment started in November 1999 and concerned the only first 180 patients enrolled in ISAARV. In May 2004, adherence assessment began for the other 224 patients and therefore, measurement was missing for at least the first 2 years of their therapy (late entry in adherence cohort).

To obtain their antiretroviral drugs, patients had to go to a single dispensing site (Fann Hospital). There, patients not included in the initial trials paid according to their incomes and got their tablets. In November 2000, a drastic cut in price (about 75%) was negotiated with pharmaceutical companies under the aegis of UNAIDS, and since December 2003, treatment is free for all patients. The dispensing procedures and support measures, such as social and financial support, counseling, and access to discussion groups were the same for all patients.

During patients' visits to the dispensing site, adherence assessment was conducted by the dispensing pharmacist. He counted the returned pills and interviewed the patient using a structured questionnaire to ask about reasons for nonadherence.

For each antiretroviral drug, adherence was calculated as the ratio between the number of tablets estimated as taken and the number of tablets prescribed. Then, we defined overall adherence for the past 30 days as the arithmetic mean of adherence of each antiretroviral drug.

Statistical Analysis

Data were censored at death or last visit before April 20, 2009. Good adherence is defined as an adherence $\geq$95%. Baseline characteristics of the patients in the 2 parts of the cohort were summarized using descriptive statistics and compared using χ^2 test for categorical variables and Wilcoxon test for continuous variables. Annual estimates of mean adherence and proportion of good adherents were calculated.

To confirm the relevance of our adherence measurement tool, the relationship between good adherence and viral reduction over the first year on HAART was analyzed among the HAART-naive patients using a Wilcoxon test.

Studied factors included age at baseline, gender, CD4 cell count at baseline, body mass index, CDC stage, Karnofsky scale, time since HAART initiation, indinavir (IDV)-based regimen, patient financial participation, and cotrimoxazole prophylaxis taken besides HAART. A Tobit mixed model for repeated measures with a random intercept was fitted to identify predictors of adherence.[20,21] All factors except age, baseline CD4, and gender were considered as time dependent.

We also fitted a latent class model with a latent variable characterizing different patterns of good adherence trajectories over time.[22] This method aims to identify the principal determinants of good adherence and typical latent adherence trajectories based on individual adherence responses over time. These trajectories were modeled using a polynomial function of time on HAART. The model then estimated the membership probabilities for each patient and a unique latent trajectory was assigned to a patient based on the maximal membership probability. It is important to highlight that each patient has his/her own behavior regarding adherence over time, hence one trajectory does not describe entirely a given patient's adherence behavior. Different models were fitted and compared with the likelihood ratio test.

Finally, we performed a survival analysis using a Cox proportional hazards model to explore the link between adherence trajectories over time and mortality for patients on HAART. The Schoenfeld residuals were tested to check the proportional hazards assumption.

All analyses were performed with Stata 10 software (Stata Corporation, College Station, TX), using the generalized linear latent and mixed model (GLLAMM) framework.[23] The threshold P value to include factors in an initial model was 0.4 and 0.05 for all other tests.

Ethical Review

This research received an ethical clearance from the Senegalese MoH/Conseil National de la Recherche en santé under the n° 0017 MSP/DS/CNRS on April 9, 2009 and an administrative clearance from the MoH/"Direction de la santé" under the n° 0760 MSP/DS/CNRS on April 10, 2009. All patients gave their written informed consent.

RESULTS

A total of 404 patients were eligible for inclusion. Adherence data were missing for 74 patients mostly due to the early death of 60 of them, before adherence assessment. Therefore, adherence data were available for 330 patients accruing 11,944 person-month. Table 1 presents patients' baseline characteristics. In the cohort of patients included in May 2004, there were significantly more women, and patients had a lower baseline viral load. Among the 330 patients included in the adherence analysis, 146 were men and 184 were women (female to male ratio, 1.3:1). The median age was 37 years [interquartile range (IQR), 31–43], and 41% of the patients were in CDC stage B and 54% in CDC stage C. At enrollment, the median viral load was 5.2 $\log_{10}$ copies per milliliter (IQR, 4.7–5.6) and the median CD4 cell count was 139 cells per microliter (IQR, 61–224).

Initial HAART regimen was a triple-drug combination made up of 2 nucleoside reverse transcriptase inhibitors + 1 nonnucleoside reverse transcriptase inhibitor or 1 protease inhibitor (PI). The 4 main regimens were stavudine-didanosine-indinavir (18%), lamivudine-didanosine-efavirenz (17%), lamivudine-zidovudine-indinavir (14%), and stavudine-didanosine-efavirenz (13%). Indinavir was the most prescribed PI, and 39% of initial regimens contained indinavir. A cotrimoxazole prophylaxis was prescribed to 76% of patients at the beginning of their therapy.

Adherence was recorded until April 20, 2009. The median treatment duration was 91 months (IQR, 84–101). The average interval between 2 visits was 1 month and 24 days and 88.5% of adherence measures were recorded with less than a 2-month interval. After 5 years on HAART, only 13 patients were lost to follow-up.

Over the study period, mean adherence was 91.2% [95% confidence interval (CI), 90.8% to 91.6%], and proportion of good adherents was 74.8% (95% CI, 74.0% to 75.6%). Mean monthly adherence decreased during the first 3 years, reaching 90.8% (95% CI, 89.8% to 91.8%) during the fifth year and thereafter tended to stabilize about 91%. Good adherence followed the same trend, fluctuating between 60% and 95%, attained 69.8% (CI 95%, 67.5% to 72.0%) in the fifth year and then stabilized about 70%.

Over the first year on HAART, among the naive patient subsample (n = 111), the decrease in viral load among good adherent patients was larger than that among the less adherent patients (3.18 $\log_{10}$ copies per milliliter vs. 2.57 $\log_{10}$ copies per milliliter; $P = 0.04$), underlying the ability of our measurement tool to approximate the true adherence.

The results of the multivariate Tobit regression are summarized in Table 2. Every year, adherence declined on average by 7%. Patients who took an IDV-based regimen had, on average, an adherence about 30% below other patients, although it rose by 4% each year (significant interaction term). Taking a cotrimoxazole prophylaxis besides HAART increased adherence of about 12%. The random intercept was significant ($P < 0.001$), and variance due to patient represented 25% of the total variance ($\rho = 0.25$), suggesting a large heterogeneity among patients.

Factors associated with good adherence identified by the LCA are presented in Table 3. Both linear and quadratic time trends were significant, respectively, decreasing and increasing. IDV-based regimen showed a significant detrimental effect on good adherence, whereas cotrimoxazole prophylaxis taken besides HAART was significantly associated with a better adherence. In addition, there was a significant gender effect with better adherence for women. Three typical latent trajectories of adherence were revealed (Fig. 1). The first latent trajectory represented 23% of the patients falling into the lowest adherence behavior class with a probability of being good adherent fluctuating between 0.4 and 0.6. The second latent trajectory represented 48% of the patients falling into an intermediate adherence behavior class with a probability of being good adherent decreasing until the fourth year on HAART and then stabilizing about 0.7. Finally, the third latent trajectory represented 29% of the patients who fell into the highest adherence behavior class with a probability of being good adherent constantly greater than 0.85.

Over the study period and among the 330 patients included in the adherence analysis, 53 patients (16.1%) died in a median time of 44 months (IQR, 19–68). The Kaplan–Meier estimates of mortality differed strongly by the latent adherence

TABLE 1. Baseline Characteristics of Patients from the Original Cohort and of the Patients Included in May 2004, Senegal, 1998–2009

Characteristics	Original Cohort (n = 158)	Included in May 2004 (n = 172)	*P*	Overall (n = 330)
Age, yr				
Median (IQR)	38 (32–43)	37 (30–43)	0.43	37 (31–43)
Gender (n (%))				
Men	79 (50.0)	67 (39.0)		146 (44.2)
Women	79 (50.0)	105 (61.0)	0.02	184 (55.8)
CD4 (cells/μL)				
Median (IQR)	136 (61–217)	145 (61–228)	0.83	139 (61–224)
<50	35 (22.3)	37 (22.3)		72 (22.3)
50–199	73 (46.5)	71 (42.8)		144 (44.6)
200–349	38 (24.2)	49 (29.5)		87 (26.9)
≥350	11 (7.0)	9 (5.4)		20 (6.2)
Viral load ($\log_{10}$ cp/mL)				
median (IQR)	5.3 (4.8–5.7)	5.0 (4.6–5.4)	<0.001	5.2 (4.7–5.6)
CDC stage				
C	88 (55.7)	90 (52.3)	0.80	178 (53.9)
B	61 (38.6)	73 (42.5)		134 (40.6)
A	9 (5.7)	9 (5.2)		18 (5.4)

TABLE 2. Determinants of Adherence Identified by the Tobit Mixed Model, Senegal, 1998–2009

Determinants	Coefficient	95% CI
Time since HAART initiation, yr	−6.66	−8.26 to −5.06
IDV-based regimen	−30.03	−36.37 to −23.69
Time by IDV-based regimen	4.19	2.87 to 5.52
Cotrimoxazole prophylaxis besides HAART	11.67	8.74 to 14.60
Random effect	ρ = 0.25*	

*Proportion of the total variance contributed by the patient-level variance.

TABLE 3. Determinants of an Adherence ≥ 95% and Percent of Patients in Each Latent Class Identified by the Latent Class Analysis, Senegal, 1998–2009

Determinants	Odds Ratio	95% CI
Time since HAART initiation, yr	0.73	0.67 to 0.79
Time since HAART initiation squared, yr	1.21	1.13 to 1.29
IDV-based regimen	0.38	0.29 to 0.51
Time by IDV-based regimen	1.16	1.09 to 1.24
Cotrimoxazole prophylaxis besides HAART	1.51	1.32 to 1.74
Gender (F vs. M)	1.37	1.17 to 1.61
Latent Adherence Trajectories		**% Patients**
Low adherence trajectory		23
Intermediate adherence trajectory		48
High adherence trajectory		29

TABLE 4. Adjusted Mortality Rate Ratios (95% CI) from a Cox Proportional Hazards Model, Senegal, 1998–2009

Predictors*	HR†	95% CI
Latent adherence trajectories		
Intermediate adherence trajectory	0.38	0.21 to 0.69
High adherence trajectory	0.12	0.04 to 0.34
Female gender	0.47	0.26 to 0.84
CD4 at HAART initiation ≥ 200 cells/μL	0.41	0.18 to 0.92
Hemoglobin level at HAART initiation (g/dL)‡	0.85	0.72 to 0.99

*Reference groups: low adherence trajectory; male gender; CD4 at HAART initiation < 200 cells per microliter, respectively.

†Global χ^2 test on Schoenfeld residuals: $P = 0.67$; detailed χ^2 on latent adherence trajectories: $P = 0.94$, $P = 0.92$; gender: $P = 0.57$; CD4 at HAART initiation: $P = 0.1$; hemoglobin level at HAART initiation: $P = 0.58$.

‡Continuous variable.

trajectories (log rank test: $P < 0.001$). The multivariate Cox model showed that latent low adherence behavior over time, male gender, baseline CD4 cell count < 200 cells per microliter, and low hemoglobin level at HAART initiation were independently associated with a higher mortality rate (Table 4).

DISCUSSION

This long-term analysis of adherence among the first Senegalese adult patients put on HAART between 1998 and 2002 suggests an overall mean adherence stabilized at about 91% with approximately 75% of the patients taking more than 95% of the prescribed drugs. The time trends and worsening effect of IDV-based regimen have already been described on a subsample of that cohort, but new determinants of adherence, such as cotrimoxazole prophylaxis and female gender, are revealed. Moreover, the innovative LCA suggests that the data are compatible with 3 types of adherence behaviors over time: high, intermediate, and low. Finally, the survival analysis highlights the link between adherence behavior and mortality and reveals a higher mortality among men.

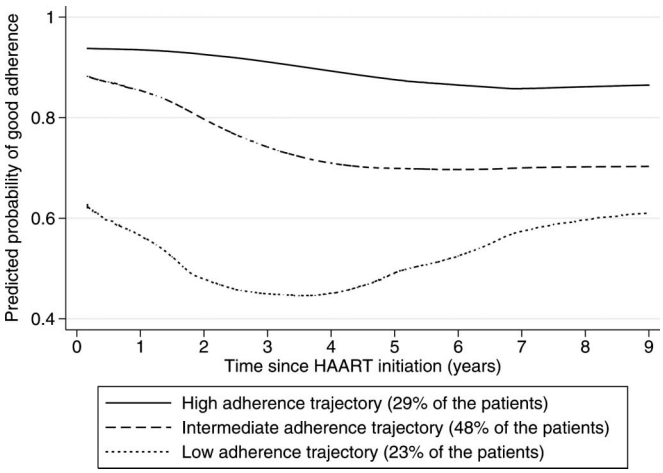

FIGURE 1. Latent trajectories of the probability to be good adherent, Senegal, 1998–2009. Predicted probability of good adherence as a function of duration on HAART by latent class.

The first result is the sustained high level of adherence during the 9 years on HAART, with a mean adherence about 91% and a mean proportion of good adherents about 75%. These results are in line with a meta-analysis, including 27 sub-Saharan studies, which reported a pooled estimate of 77% of good adherent (95% CI, 68% to 85%).[24] Another study conducted in Uganda, in a retrospective cohort of 897 patients, between May 2004 and December 2006 reported that 78.2% of patients were good adherent (95% CI, 75.3% to 80.8%).[25] A similar estimate has also been obtained from a prospective study in Ivory Coast.[26]

The study of the Antiprotéases Cohorte (APROCO) cohort shows that adherence is a dynamic process,[14] and the decline in adherence over time has already been reported in midterm follow-up.[27,28] Our study, unique in its long follow-up, confirms a long-term decreasing trend in adherence for patients still on treatment.

Our previous reports underline PI-containing regimen as a factor associated with worse adherence.[17,18] This updated analysis on a larger number of patients and longer follow-up confirms, in the long term, a lower adherence for patients who receive indinavir. Other studies report that PI-based regimen, especially indinavir, is responsible for nonadherence, probably because of the side effects and the complexity of taking the treatment.[29–31]

Our study points out a better adherence for patients who took cotrimoxazole prophylaxis besides HAART. This new result is also reported in a cross-sectional study in Ethiopia among pediatric patients.[32] Cotrimoxazole prophylaxis started before HAART can provide a therapeutic education for patients, enabling them to be good adherents.[32,33] Moreover, the Desmond Tutu HIV Foundation suggests starting a cotrimoxazole prophylaxis a month before starting HAART to improve adherence and affirms that adherence to cotrimoxazole is a good indicator of adherence to antiretroviral treatment.[34] In our study, an alternative explanation could be that once cotrimoxazole is stopped by the physician when CD4 level exceeded 500 cells per microliter, patients become less adherent to ARV drugs because they feel better and experience less HIV-related events.

The LCA identified 3 patterns of adherence. We show that a quarter of patients experience a high adherence trajectory,

a quarter of them a low adherence trajectory, and about half of the patients an intermediate adherence trajectory. This important proportion of patients with an intermediate adherence trajectory is alarming because viral replication could be active, and patients are at risk to develop a resistance to antiretroviral drugs. These long-term adherence patterns question the assumptions of the "treatment as prevention" approach assuming no different levels of adherence and a low long-term dropout rate (1.5% per year).[35] The determinants of good adherence are the same in all latent classes, but none of these factors could predict belonging to a specific class. A gender effect is also revealed by the LCA, women being more adherent, irrespective of the latent adherence pattern. In the literature, gender is generally not associated with adherence.[8,13,36] However, comprehensive studies have shown that women make better use of health care facilities than men in West Africa and communicate more with health care workers on disease and treatment issues.[37,38] Other studies have reported that women are more likely to attend health services and to start HAART than men in resource-limited settings.[39,40] The dedicated provision of reproductive and child health care may explain the better attending of health structures by women. Furthermore, the stigma of HIV infection, work and family responsibilities, and homophobia could make the acceptance of HIV diagnosis and treatment more difficult for men. These results argue that men's vulnerability regarding access to HAART and adherence should be considered and studied.

A recent study of the Swiss HIV cohort has also identified different patterns of adherence over time with a group-based trajectory model.[41] Although this method is similar to LCA, their results are based on self-reported adherence with ordinal responses. The strength of our approach is that it reveals the predictors of good adherence along with the latent trajectories based on quantitative responses.

The survival analysis reveals a strong association between patients' adherence and mortality on HAART, showing a higher risk of death for the patients with low adherence behavior. The link between adherence and mortality has been well documented.[25,42,43] In this study, we use the identified latent classes as predictors of mortality to analyze the link between adherence behaviors over time on HAART and mortality. To our knowledge, such a method to explore the effect of adherence on mortality was never used before and confirms the importance of adherence to HAART. In addition, a higher mortality is observed among men irrespective of the pattern of adherence over time. This result raises the problem of treatment access for men and confirms the hypothesis of a better use of health care structures by women.

As many studies in sub-Saharan Africa have shown, cost of drugs is one of the main reasons for nonadherence.[44–47] Indeed, our first report on a smaller number of patients and shorter follow-up duration confirmed a link between financial participation and poor adherence.[18] Since antiretroviral treatment became free in December 2003, patient financial participation is no longer associated with adherence in this extended follow-up duration from November 1999 to April 2009.

Many methods are available to measure adherence, but none of these methods are ideal. Two different methods to assess adherence are recommended, with one including patient statements.[48] In this study, we combined a quantitative approach and a qualitative approach to assess adherence: a pill count and a face-to-face interview conducted by the dispensing pharmacist. This approach is well adapted to sub-Saharan Africa as it is both simple and inexpensive.[48,49] However, it is important to note several limitations. First, interviews are human resource demanding, and they required 15 to 30 minutes to ensure good quality data.[16] Interviews also tend to overestimate patient adherence and can be affected by how questions are asked (interviewer bias). Moreover, pill count may also overestimate adherence because patients can discard or simply forget some remaining pills.[50] As there is no gold standard to measure adherence, assessment tools have to be adapted. In general, a correlation between adherence and virologic response for HAART-naive patients during the first month of therapy tends to confirm the relevance of the tool.[48] Such a correlation has been found in our study 1 year after HAART initiation. A second limitation is the absence of adherence data for 74 of the 404 eligible patients, which can bias the estimated overall level of adherence of the cohort. More than three-fourth of these 74 patients died before any adherence measurement, at an early stage of the disease, because of an impaired clinical status. Judgment on the direction of a potential bias on adherence over the first year on treatment remains uncertain.[51] However, the strengths of our study are the high frequency measurement (on average, 1 month 3 weeks), the large number of repeated measures per patient, and the long follow-up, which gives a better subject-specific estimation of adherence.

In conclusion, this study shows that good adherence can be maintained in the long term in sub-Saharan Africa. This is largely due to the initiative of the Senegalese government and association backing, which helped to ensure rigorous follow-up providing strong support for adherence. The nature of the regimen deserves special attention, and the cotrimoxazole prophylaxis as a marker of good adherence should be explored further. Our analysis also highlights an important heterogeneity between patients. The 3 latent adherence trajectories and the gender effect suggest that different support measures can be introduced to improve adherence, in particular among the intermediate adherent group to avoid emergence of resistance and that men should receive special attention.

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design of the study and the interpretation of the results, reviewed the manuscript, and approved the final version. R. Ecochard contributed to the analysis of the data and the interpretation of the results, reviewed the manuscript, and approved the final version. P. S. Sow contributed to the design of the study, reviewed the manuscript, and approved the final version. E. Delaporte contributed to the design of the study and the interpretation of the data, reviewed the manuscript. and approved the final version. J-. F. Etard directed the research, contributed to the design of the study, the analysis of the data. and the interpretation of the results, reviewed the manuscript. and approved the final version.

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APPENDIX 1: ANRS 1215 STUDY GROUP

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