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**Adherence to antiretroviral therapy in patients enrolled in a comprehensive care
program in Cambodia: a 24-month follow-up assessment**

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ABSTRACT

Objectives: The long-term maintenance of adherence remains an important issue, especially in limited-resource settings where additional barriers exist. A cross-sectional study was performed 24 months after ART initiation for patients treated in, Cambodia in order to estimate the prevalence of non-adherence and its determinants.

Methods: Adults receiving ART for 24+/-2 months were considered eligible for the study. Self-reported non adherence was defined according to an algorithm based on several different items. The questionnaire also included reported ART-related side effects and questions about HIV disclosure in the social network. HIV-1-RNA plasmatic viral load was assessed using real-time PCR. Multivariate rare events logistic regression analysis was used to identify independent factors associated with non-adherence.

Results: 346 patients participated in the survey. At 24 months (M24), 80% had a HIV-RNA below 40 copies/ml while 75% had CD4⁺ T-cell counts $\geq 200/\text{mm}^3$. The proportion of adherent patients at M24 was 95%. Virological success was significantly higher in adherent patients than in non-adherent patients (81% vs. 56%, $p=0.021$). Living in a rural area, limited HIV disclosure and perception of lipodystrophy were found to be independently associated with non-adherence to ART after two years of treatment.

Conclusion: At M24, adherence was high and explained the good virological outcomes. In order to maintain high adherence and long-term virological benefits, special attention is needed for patients with lipodystrophy-related symptoms and those who express difficulties with disclosure to their close family.

Introduction

African and Asian studies have widely demonstrated the feasibility of access to and efficacy of antiretroviral therapy (ART) in low-resource settings [1-3]. In such settings, data on long-term bio-clinical outcomes for patients on ART are still sparse and this raises the need for long-term longitudinal assessments.

Recent evidence shows that good adherence can be achieved in low-resource settings [4] while maintaining high adherence over time requires specific interventions [5] and this remains one of the greatest challenges in low resource countries [6]. In industrialized countries, especially where access to care is free, the major determinants of non adherence include treatment-related characteristics (mainly expressed by self-reported side effects), social vulnerability, depression, alcohol use or ongoing drug injection [7-12]. However though many barriers to adherence are common to both developed and developing settings, some additional contextual factors can play a major role in developing countries due to difficulty of access and socio-cultural context [4]. One of the greatest public health concerns about adherence is that sub-optimal adherence may lead to the development of drug-resistant viral strains. In addition, as adherence may change substantially over time [13] and as the existence of specific barriers to adherence in these contexts [4], maintaining adherence remains a major challenge in preventing a switch to second line regimens, whose access is still limited in low-resource settings [14].

In industrialized countries, one of the major determinants of non-adherence is self-reported side effects [7, 10]. The aim of the present analysis was to estimate the prevalence of non-adherence in Cambodian patients after two years of ART and to identify whether known factors associated with non adherence in industrialized countries (such as self-reported side effects) are also associated with reduced adherence in this setting.

Patients and methods

Médecins sans Frontières (MSF) in collaboration with the Ministry of Health of Cambodia, began a HIV program in 1997 in the infectious disease department in Khmero-Sovietic Friendship hospital in Phnom Penh. Since 2001, ART has been offered free of charge to HIV/AIDS patients *either with previous or current AIDS-defining events or with other stages* when CD4 counts $\leq 200/\text{mm}^3$ [15]. This project involved 10 physicians, 18 nurses, 4 counselors and 2 pharmacists together with training, patient education, social support and adherence consultations. To improve both the rate of patients returning to the clinic and high adherence, adherence support was performed by Khmer counsellors who were recruited and trained by MSF expatriate expert on treatment information and counselling. Before HAART initiation, patients were asked to follow 3 specific session: session 1 (S1) was organized in groups in order to deliver treatment information; session 2 was based on individual interview in which the counsellor checks patient's understanding of all information received at S1 and focused on patient's social environment to anticipate further adherence difficulties; session 3 occurred the day of HAART initiation and was devoted to discuss patient's plan to take ARV. At each HAART follow-up visit (Day 15, Month 1, M2, M3, M4, M5, M6 then after every two months), patients participated alternatively in peers groups or individual counselling session. Individual counselling sessions were delivered by a counsellor. The specificity of this counseling approach is that it explores all of the patient's problems in daily life and not simply his/her capacity to adhere to treatment [16]. The counseling team was trained according to the program used in a previous intervention trial which clearly showed that such an approach had a significant positive impact on HIV viral load [17]. Peers groups were co-chaired by a counsellor and a patient, member of a community-based association (Association of Users of ARV). Perceived non-adherence patients were asked to come more frequently at hospital. In

addition, patients who skipped any follow-up visit were systematically contacted through phone or home visit by a counsellor.

The initial first line regimen proposed was the association of stavudine, lamivudine and efavirenz. Clinical follow-up included monthly visits for the first 6 months and every 2 months thereafter. CD4 counts were monitored every 6 months but no individual viral load monitoring was available.

A cross-sectional adherence survey of patients who had been receiving ART for 24 (+/-2 months) was carried out between December 2004 and May 2005 in order to both estimate adherence 24 months after ART initiation and to evaluate its determinants. The survey also included psychosocial data collection and viral load determination, this latter being systematically offered to all patients who agreed to participate in the study

Medical data

For all patients included in the study, information regarding medical background and follow-up visits were routinely collected at each consultation on standardised forms. Medical data were collected using FUCHIA[®] software (Epicentre, Paris, France). CD4 counts were performed using flow cytometry (Facscount, Beckton Dickinson) at the Institut Pasteur in Cambodia.

Questionnaire

A face-to-face interview based on a standardized questionnaire translated into Khmer, was administered by an external member of staff. This questionnaire included several questions about patient's adherence to ART in the 4 days or the 4 weeks prior to the interview. Five

questions regarding adherence to HAART were included in all self-administered questionnaires according to the methodology established by the AIDS Clinical Trial Group [18]. Adherence to ART was assessed using a dichotomous score already validated in previous studies [13, 19]. Patients were first asked to list, for each drug included in their HAART regimen the number of pills they had actually taken on each of the 4 days before the visit. Those who reported having taken all of their prescribed doses in the 4 days before the visit were classified as adherent, unless they also reported in subsequent answers that they had skipped a dose during the previous week-end or had 'almost totally' followed their HAART regimen, or had taken all their medication at one time each day, in which case they were classified as non adherent. In addition two visual analog scales (range 1-6) respectively measuring adherence in general and in the last 4 weeks were completed: patients who reported scores <5 were reclassified as non adherent.

The questionnaire also gathered information on the patient's socio-demographics data: gender, age, marital status and place of residence. The number of self-reported side effects was determined using a French version of the symptom index for patients exposed to ART validated by Justice et al. [20] and previously used in other investigations [11, 21, 22]. This version incorporated a 20-item list of symptoms where patients were asked whether they had experienced each listed side effect at least once during the prior 4 weeks. The following symptoms were listed: nausea, abdominal pain, headaches, vomiting, diarrhoea, change in taste, heartburn, muscular pain, fever, fatigue, itching skin, sore mouth, kidney stones, insomnia, sexual dysfunction, hallucinations, bone related problems, nail related problems, hair loss and dry skin.

In addition 9 symptoms were included to measure perceived lipodystrophy: change in the body shape, larger stomach, larger breasts, slimmer legs, slimmer arms, visible veins on the legs, hollow cheeks, slimmer buttocks, accumulation of fat in the neck [19].

HIV disclosure was assessed by asking patients whether or not they had disclosed their seropositivity and to which persons in their social network. Extended or restricted HIV disclosure was dichotomized based on the fact whether the patient declared to have had informed more or less than 2 family members. Information regarding the patient-physician relationship was also collected using a 5-point Likert scale. The categories used to define the quality of the patient-provider relationship were excellent, very good, good, fair, bad. This information was split into two categories (excellent vs. other) as most individuals reported an excellent or very good relationship with their physician.

HIV viral load determination

Plasma VL measurements were performed on -80°C frozen samples at the HIV/Hepatitis laboratory, Necker Enfants Malades Hospital (Paris, France), using real-time PCR technology which allows quantification of HIV-1 non-B subtypes including those circulating in Asia [23, 24]. Positive samples from Thailand and Cambodia were studied in parallel with the Cobas Amplicor HIV-1 Monitor v1.5 Test (Roche Diagnostic Systems, Pleasanton, CA) and gave highly correlated results (data not shown).

Virolological success was defined as having a HIV RNAcp/ml lower than 40.

Statistical methods

In order to determine factors associated with non-adherence, univariate and multivariate analyses for rare events were performed. King and Zeng [25] demonstrated that conventional logistic regression underestimates the probability of rare events (such as < 5% of the data or

so). They developed corrections for the biases occurring in logistic regression when explaining such rare outcomes.

The model is estimated using rare events logistic regression [26] performed with the ReLogit package for Stata [27]. Risk-ratios and their confidence intervals were estimated by stochastic simulation using 3000 replications and the ReLogitq package for Stata [26, 28]. Variables were considered eligible for testing in the multivariate model if their p value was lower than 0.25 in the univariate analyses. The final model was built using a forward procedure based on the log-likelihood ratio test. Stepwise backward and forward procedures were used to evaluate the stability of the pattern of factors independently associated with the outcome.

The association between adherence and virological success was assessed using the Fisher exact test and quantified by computing the risk ratio and its 95% confidence interval as given by the rare events logistic regression.

Results

As of March 31 2005, 2,048 HIV-infected patients were included in the program and were receiving ART at the hospital. Among them, 416 adults had started ART two years +/- two months before the cross-sectional adherence assessment. Of these 416 patients, 53 patients died, 7 were lost to follow-up and 6 were transferred while the remaining 350 were still on ART at the time of the survey. Three patients refused to participate and one patient arrived too late to be included. A total of 346 patients were therefore included in the study.

Table 1 shows socio-demographic and medical characteristics of the patients included in the analysis. 57.5 % were male and median age was 36 years. Almost all (95.4 %) were ARV treatment naïve at ART initiation, the remaining patients having being previously exposed to

mono or dual nucleoside regimens. Most were already at an advanced stage of HIV disease when entering the program as shown by a very low median number at baseline CD4. A total of 280 patients were receiving a first line ART regimen associating d4T, 3TC and EFV while 56 were receiving d4T, 3TC and NVP and the remaining 10 another first line regimen. At M24, three quarters of the patients had CD4 counts above the 200 threshold per mm³ and 79.8% of them had viral load below 40 copies /ml. It is interesting to note that when performing an intent-to-treat analysis based on the 416 patients where those who died or were lost to follow up are assigned in the detectable viral load group, the proportion of patients with virological success is not lower than 66%.

Seventy eight percent of patients were living in the urban area of Phnom-Penh, 43.4% were not married and 80.9% had disclosed their HIV status to at least 2 family members. The median number of self-reported side effects was 3.5 while that of lipodystrophy related side effects was 2.

Among the 346 patients, only 1 patient did not take 100% of his prescribed pills in the last 4 days prior to the visit, 1 patient reported to have skipped a dose during the previous week-end, 1 patient reported to have taken all his medication at one time during the prior 4 days, 3 patients reported not to have completely followed their HAART regimen, and 13 patients reported scores <5 on visual analog scales. When computing simultaneously all questions, the final proportion of adherent patients was 95%. Despite the small number of non-adherent patients, a significant association was found between adherence as computed by the indicator based on several items and virological success. Indeed, among the 330 adherent patients, the proportion of success was 81% while this fell to 56% among the 16 non-adherent patients (RR=1.07; 95%CI [1.02-1.19]; p=0.021). Non adherence as detected by the combined indicator was the only significant predictor of virological failure whereas none of the

adherence measurements composing the indicator was significantly associated with virological failure. However non-adherence as assessed by the 2 visual analog scales only exhibited a marginal association with virological failure ($p = 0.10$).

Table 2 shows the results of the univariate and multivariate analyses. Only variables that were considered eligible ($p < 0.25$) for the final multivariate model were reported in the table. Younger age ($p = 0.25$) and female gender ($p = 0.12$) tended to be associated with non-adherence. Individuals living in rural areas ($p = 0.03$) and those unmarried ($p = 0.02$) were at a significantly higher risk of non-adherence. Patients who had disclosed their status to more than 2 family members ($p = 0.003$) or to their steady partner were significantly found to be more adherent ($p = 0.03$) to ART. Patients who reported a higher number of ART-related side effects were more likely to be non-adherent ($p = 0.06$).

The final multivariate analysis (Table 2) shows that three factors were found to be independently associated with a greater risk of non-adherence after two years of treatment: living in rural areas ($p = 0.036$), disclosing one's HIV status to 2 family members or less ($p = 0.002$) and reporting a higher number of lipodystrophy-related side-effect ($p = 0.036$).

Discussion

The major result of this analysis carried out for Cambodian patients at the end of their second year of ART is the high proportion of adherent patients in this population. Such favorable outcomes are even higher than those reported in western cohorts but similar to those reported in a previous study carried out in Malawi by MSF [29]. The proportion of highly adherent patients is also greater when compared with a meta-analysis of published studies on

adherence to ART which found that 55% of North American patients (range: 26%-86%) and 77% of African patients (range: 30%-100%) achieved optimal adherence [30]. This result could be predictable considering the extreme severity of the disease at ART initiation for the patients included in the present study and patients with advanced HIV disease are more likely to be adherent as asymptomatic patients [31]. Intensive patient education, counseling and ongoing psychosocial support might all explain the low rate of lost to follow-up observed in this program and the very low rate of non-adherence. “Interestingly, the staffs involved in adherence education and counseling were trained by the same team which obtained high adherence rates after implementing the same approach of patients education and counseling in French patients [15-16]. However, the effect of ART rationing on patient motivation, 'early adopter' effects during the initial phase of ART scale-up and socio-cultural factors may also have contributed to increase adherence in such a population, though these possible causes could not be assessed in this study.” Despite the small number of cases reporting non-adherence, there was a statistical relationship between non-adherence and virological failure. As already shown in other studies using a similar method of questioning [29], these results suggest that patients' reporting is a simple way to measure adherence especially once desirability bias has been minimized by guaranteeing anonymity and using staff external to the hospital to interview patients.

As for industrialized countries [19], the study highlighted the linear relationship between an increasing number of ART-related side effects and non-adherence. Although both lipodystrophy and non-lipodystrophy related symptoms were associated with non-adherence in univariate analysis, only lipodystrophy-related symptoms remained associated with the outcome in the multivariate model. In this specific context, such symptoms which represent visible physical marks could be over-reported and be a proxy of fear of stigmatization. Such a

fear could contribute to non adherence behaviors. It has already been shown that perceived lipodystrophy symptoms affect psychosocial well being and increase the stigma associated with the disease [32]. This may explain why lipodystrophy-related symptoms contribute more to non-adherence than other general symptoms. An important predictive factor of non-adherence to ART is living in a rural area. As already documented in industrialized countries [33, 34], this factor is a proxy for the difficulty in access to hospital departments (and access to ART medication) both in terms of distance and socio-economic costs of transport. This factor is significant despite the limited number of non-adherence events and clearly shows the need for decentralization of care. This result suggests that decentralization of care should be implemented as soon as possible or when this is not feasible, other models for delivering care should be investigated as the use of mobile care units in rural areas in order to increase access and adherence to ART in low-resource settings.

Limited disclosure of HIV status in the patient's social network was also found to be associated with non-adherence as already reported in other studies carried out in different settings. These studies have shown higher rates of adherence in patients who reported greater serostatus disclosure [35, 36]. Interestingly, the impact of disclosure on adherence has detrimental effects when disclosure is uncontrolled.[37].

Difficulties in disclosing HIV status to members of one's social network may be mediated by the social stigma against HIV disease in the patient's community. Despite the fact that counseling for disclosure difficulties and the management of stigma were already integrated in the comprehensive care package of the care program described in this paper, further action at society level is needed to increase the acceptance of HIV disease in all communities.

Moreover, interventions to improve ART adherence should address the role of serostatus disclosure by providing patients with skills to maintain adherence.

The major limitation of this study is its cross-sectional nature with a unique point estimate of adherence being correlated with outcomes after two years of ART. Patients who reported being adherent in the present analysis may have experienced episodes of non-adherence in the past as adherence is a dynamic process [13]. It is possible that patients who were non-adherent and virologically suppressed may have been highly adherent during the induction of treatment and this may be enough to explain their virological success as already shown in a previous study [38]. In addition, one cannot exclude the possibility that the selected group may under-represent non-adherent patients, who are at a higher risk of death or of being lost to follow-up. However, the proportion of patients who died or were lost to follow-up in the present study is relatively low despite the severe patients' immunodeficiency at ART initiation.

Another limitation of the study is that adherence assessments are only based on self-report. Self-report is an appropriate tool when used in an observational setting in a developing country. However in this study it may have induced over-reporting of adherence, as already described in previous literature [39]. Such a bias is likely to limit the specificity of the measurement of adherence in a similar way to that previously reported in industrialized countries' settings. Although using a dichotomous score did not enable us to calculate true adherence, it was useful for improved detection of non-adherent patients thanks to the addition of specifically related questions. Although the accuracy of the instrument could not be assessed using plasma dosages or other methods for collecting adherence due to the context where the study was conducted, it is important to note that the combined score was however, more powerful to detect virological failure than each single measure of adherence.. A meta-analysis by Nieuwkerk and Oort has already shown the validity of self-reported

measures of adherence [40]. In addition we used an algorithm that has been already validated with plasma detection of PI in other cohort analyses [41, 42]. This algorithm is based on the principle that self-reported adherence is affected by social desirability and that to better identify adherent patient we classify as non adherent all those who reported non adherence at least in one of the items of the adherence questionnaire.

The results of this study may have important methodological and public health consequences. Firstly, these results confirm that the measures of adherence based on self-report can be successfully transferred to low-resource settings. Secondly, the levels of adherence found in this study were extremely high, and much higher than those reported by patients living in developed countries. Finally, such high levels of adherence suggest the importance of a comprehensive package of care based not only on ART provision but also on patient's education, peer support and psychosocial counseling on adherence. Interventional research to rapidly scale up ART delivery should take into account the inclusion of similar models of comprehensive care especially in the process of decentralization of care services.

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Table 1. Medical and socio-behavioral characteristics of patients at the time of cross-sectional adherence assessment, Cambodia M24 Cohort, n = 346			
	N	%	Median [IQR]
Men	199	57.5	
Age			36 [32-40]
ARV naïve at ART initiation	330	95.4	
CD4 counts/ mm³ at ART initiation			17 [4-74]
Current ARV treatment			
3TC / d4T / EFV	280	80.9	
3TC / d4T / NVP	56	16.2	
Others	10	3	
CD4 counts/ mm³ at M24			274 [199-371]
CD4 counts/ mm³ > 200 at M24	259	74.9	
% HIV RNA <40 cp/ml at M24	276	79.8	
Living in rural area °	75	21.7	
Unmarried	150	43.4	
Restricted HIV disclosure to his/her family #	66	19.1	
Not having disclosed HIV status to their partner	139	40.0	
Not having disclosed HIV status to their child(ren)	202	58.4	
Not having experienced change in body shape	189	54.6	
Good relationship with health care provider	265	76.6	
Number of self-reported side-effects ☒			3.5 [2-6]
Number of lipodystrophy-related side-effects			2.0 [1-4]
Adherent patients	330	95.4	

Restricted HIV Disclosure was dichotomized based on whether the patient declared to have had informed none or just one family member (mother, father, partner, child)

☒ Excluding lipodystrophy related symptoms

° Living in a rural area was defined as living in villages or small towns outside the Phnom Penh area

Table 2 : Factors associated with non - adherence, rare events logistic model, Cambodia, M24				
Cohort n = 346				
	Univariate analysis		Multivariate analysis	
	RR*	95%CI	ARR**	95%CI
Female gender	1.04	0.99-1.10		
Age<35	1.03	0.99-1.08		
Living in a rural area	1.07	1.01-1.17	1.11	1.02-1.34
Unmarried	1.07	1.02-1.12		
Restricted HIV disclosure to his/her family #	1.11	1.04-1.24	1.13	1.04-1.37
No HIV disclosure to his/her partner	1.06	1.02-1.13		
No HIV disclosure to his/her mother	1.09	1.00-1.31		
No HIV disclosure to his/her child(ren)	1.03	0.99-1.08		
Number of self-reported side-effects §¤	1.004	1.001- 1.006		
Number of lipodystrophy-related side-effects §	1.006	1.004- 1.010	1.035	1.010-1.076

§ For continuous variables, crude and adjusted RRs were calculated per unit increase

¤ Excluding lipodystrophy related symptoms

Restricted HIV Disclosure was dichotomized based whether the patient declared to have had informed no or just one family member (mother, father, partner, child)

° Living in a rural area was defined as living in villages or small towns outside the Phnom Penh area

* Risk ratio estimates.

** ARR (Adjusted risk ratio) and CI (confidence interval) were obtained from 3000 simulations of “relogitq” for Stata program.