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Original article

Adherence to oral antibiotic therapy in patients with bone and joint infection: A pilot study☆

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ABSTRACT

Objectives: The management of bone and joint infections (BJI) is complex and requires prolonged antimicrobial therapy. Few data exist on adherence to anti-infectious treatment other than HIV, and none on BJI, even though compliance is considered as a major determinant of clinical outcome. This work aimed at evaluating adherence to oral antimicrobial treatment in patients with BJI.
Patients and methods: This is a prospective observational blinded pilot study evaluating adherence by a 6-item questionnaire at 6 weeks (W6) and 3 months (M3) post-surgery. The primary endpoint was the proportion of patients with high, moderate and poor adherence at W6. Secondary endpoints included change in adherence between W6 and M3, and the exploration of potential variables influencing adherence.
Results: Analysis was performed on 65 questionnaires obtained from 43 patients including 35 with device-associated BJI. At W6, 11 out of 34 patients were highly adherent to oral antibiotic therapy, 22 moderately adherent and 1 poorly adherent. There was no significant change in adherence to antibiotic therapy between W6 and M3. The only variable significantly associated with the level of adherence at W6 and M3 was the number of daily doses of antibiotic ($P = 0.04$ and 0.02 at W6 and M3, respectively).
Conclusions: This study provided a snapshot of patients' adherence in BJI. Adherence to antibiotic therapy appeared to be stable up to 3 months and a higher number of daily doses of antibiotic was associated with poorer adherence. These observations need to be confirmed in future large-scale studies using electronic pill monitoring systems.

1. Introduction

The World Health Organization has defined adherence to long-term therapy as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [1]. Adherence not only considers medical prescriptions but refers to more global patient behavior towards a therapeutic strategy [2].

Adherence to drug therapy has been studied for a number of chronic diseases including HIV infection, depression and hypertension [3,4]. Limited information exists about drug adherence to antibiotic therapy, and available data are limited to short-term antibiotic treatments [5]. Good adherence has been associated with more favorable clinical outcomes and lower mortality in a variety of chronic and acute diseases [6,7]. For infectious diseases, poor adherence may heighten the risk of therapeutic failure and re-infection, facilitate the emergence of resistance and increase healthcare costs due to relapses of infection and subsequent hospitalizations [8,9]. Determinants of poor adherence to drug therapy include factors related to the medication itself (such as dosing regimen or adverse drug reactions), to the patient (knowledge and beliefs about pathology and drugs), to the disease (clinical symptoms, potential complications) and to the patient-physician relationship [10,11]. It is interesting to note that good adherence

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to placebo has also been associated with a lower risk of mortality [6]. Last but not least, adherence to drug therapy may be a sign of an overall healthy behavior, the so-called healthy adherer effect.

Bone and joint infections (BJI) are bacterial infections that can occur on native joints or be device-associated. In France, they represent a significant cause of morbidity and occasional mortality, and a major source of healthcare expenditures [12]. Management of BJI usually requires both surgical and medical management, the latter including intravenous or oral antimicrobial therapy. The duration of antimicrobial treatment for BJI may range from 6 weeks to several months in the event of more complicated infections [13]. All in all, antibiotic therapy of BJI is substantially longer than that of most infections. Lengthy duration may be a risk factor for poor adherence. Besides its prolonged duration, antimicrobial treatment may require multiple daily doses of several antibiotics and be responsible for serious adverse events [14]. Based on previous study results, these different characteristics also raise concerns about adherence [11,15].

To our knowledge, no study has assessed the adherence to antibiotic therapy in patients with BJI. Prevalence, adherence patterns over time and determinants of adherence in this population are not known. Currently, drug adherence is not routinely evaluated and is not considered in the treatment of BJI in our center.

The aim of this work was to evaluate adherence to oral antimicrobial treatment in patients with BJI. The secondary objectives were to investigate variations of adherence during treatment, and to identify factors influencing drug adherence to antibiotics in this setting.

2. Patients and methods

This is a prospective observational blinded pilot study evaluating adherence to oral antibiotic therapy in patients with BJI. The study was monocentric and did not involve any additional medical procedure compared to the usual management of patients with BJI. Evaluation of adherence by a questionnaire was the only procedure added. So as to avoid interfering with patient management, the results of this evaluation were not communicated to practitioners. Patients were informed and their consent was required to participate. This study was approved by an ethics committee (CPP Sud-Ouest and Outre-mer on October 13th, 2017). The study was registered on the clinicaltrials.gov website (NCT03311113).

Adherence to treatment was assessed by a questionnaire adapted from the French standardized self-administered questionnaire put together by Girerd et al. [16], a 6-item questionnaire classifying patients as highly adherent, moderately adherent or poorly adherent (Appendix 1).

Inclusion criteria were as follows: age $\geq$ 18 years, informed consent, affiliation to French social security, diagnosis of BJI with surgical and medical management in our center, therapy involving at least one oral antibiotic for a minimum duration of 6 weeks. Exclusion criteria included antibiotic therapy for BJI without a defined duration (i.e. chronic or suppressive therapy), antibiotic therapy administered by parenteral route only, absence of phone number or opposition to communication by phone, physical or mental disability impeding information and consent as well as communication by phone.

In our center, the usual management of patients with BJI proceeds as follows. Surgery is performed and considered as the start of follow-up (Day 0). An initial course of antibiotic is administered at Day 0. Most often, a combination of two intravenous antibiotics is administered, with a broad spectrum of activity, for example cefepime combined with vancomycin. The first follow-up visit is planned between 15 and 21 days post-surgery. Antibiotic treatment is often modified at this point, based on microbiology analysis of samples collected during surgery. A switch from IV to oral antibiotic is performed whenever possible. A second follow-up visit is planned 6 weeks post-surgery and a third follow-up visit occurs 3 months post-surgery, if necessary. Additional visits are possible in case of adverse events, poor clinical outcome, hospitalization, or antibiotic treatment prolonged after 3 months.

In the study, patients were usually recruited at the first follow-up consult (Day 15–21 post-surgery), after information and collection of their consent. Data collected at inclusion were: sex, height, weight, year and month of birth, age, level of education, professional status, place of care or living place during treatment, family status, presence of caregiver, ASA (American Society of Anesthesiologists) score, site of BJI, start date of symptoms, and presence of implant. We also recorded the usual treatment of the patient (molecule, route of administration, dosage) and the characteristics of antibiotic treatment (molecule, starting date, route of administration, dosage, date of therapy end).

Assessment of medication adherence occurred within the week before or after visits planned at week 6 (W6) and month 3 (M3) if the patient was still under antibiotic treatment at that time. It was performed by a standardized questionnaire delivered by phone by a pharmacist. We used a modified version of the Girerd questionnaire, which is recommended by the French national medical insurance system (*Assurance Maladie*) as a means of monitoring adherence in clinical routine. The questionnaire was modified to mention "antibiotic(s)" (*antibiotique(s)*) instead of the general term "drug(s)" (*medicament(s)*). Presented in Appendix 1, the questionnaire includes 6 questions and yields an adherence score ranging from 0 to 6 points. A score of 6/6 indicates high adherence and scores of 5/6 and 4/6 indicate moderate adherence, while a score ≤ 3 is interpreted as poor adherence to oral antibiotic therapy.

After follow-up visits at W6 and M3, additional data were collected from the patients' medical files: clinical evolution, modification of the usual treatment, modification of antibiotic treatment (molecule, start date, route of administration, dosage, date of therapy end), adverse events. All data were manually collected in a hard copy file and then recorded in a dedicated Access® database.

The primary endpoint was the proportion of patients with high, moderate and poor adherence at W6. As a secondary endpoint, we evaluated change in the proportion of patients with high, moderate and poor adherence between W6 and M3, among patients who received at least 3 months of antibiotic therapy. Proportions were compared with Mc Nemar test for paired samples with p-value set at 5%. We also investigated potential variables influencing adherence to antibiotic therapy. Patients with moderate and poor adherence were pooled and their characteristics were compared with those of patients with high adherence. The Wilcoxon–Mann Whitney test and the Fisher exact test were used for quantitative and qualitative variables, respectively, with *P*-value set at 5%. For variables associated with adherence based on this analysis, a univariate logistic regression was performed to identify potential predictors of high adherence. Variables were included as binary or continuous. Logistic regression enabled us to calculate odds-ratio of high adherence for the variables tested along with their confidence interval and statistical significance based on the Wald test, with *P*-value set at 5%. Multivariate regression was not performed because of the limited sample size and an insufficient ratio of events per variable. Statistical analysis was performed with the Statview software (SAS institute, Cary, NC, USA).

As this was a pilot study, sample size was not statistically determined. We planned to include 60 patients within a year in order to obtain an acceptable representation of the center's patient cohort (about 400 newly diagnosed patients with BJI per year). Patients were recruited between November 2017 and November 2018.

Table 1
Patient characteristics.

	$n = 43$ patients
Gender	
Men	29
Women	14
Age (years, mean ± SD)	61 ± 15
Site of infection	
Lower limb	35
Upper limb	3
Spine	2
Face	3
Device-associated infection	
Yes	35
No	8
Level of education	
Primary school or no school	8
Pre-baccalaureate level (French BEP, BEPC, CAP)	13
Baccalaureate	6
University degree or equivalent	16
Professional status	
Sick leave	12
Invalidity	1
Retired	24
Active	4
Unemployed or job seeking	2
Place of care	
Home	13
Home hospitalization	7
Conventional hospitalization	6
Rehabilitation center	17
Family status	
Single	4
Married or free union	30
Divorced	6
Widow	3

3. Results

Sixty-three patients were recruited for the study but in the final analysis data from only 43 of them were retained. Twenty patients were excluded for the following reasons: current antibiotic therapy shorter than 6 weeks ($n = 10$), complications requiring multiple surgeries and parenteral antibiotics ($n = 3$), no answer to phone call ($n = 2$), no antibiotic treatment prescribed after recruitment ($n = 2$), decision of chronic antibiotic treatment during therapy ($n = 1$), no scheduled follow-up visits and no information in medical file ($n = 1$), and same patient included twice in the study ($n = 1$). The large number of exclusions may be explained by the complexity of BJI management. Antibiotic therapy is only part of the patient care and the planned treatment strategy needs to be adjusted in some patients after surgery. Patient characteristics are presented in Table 1.

A total of 67 adherence questionnaires were collected from the 43 patients. Three questionnaires were inadvertently administered at follow-up visit between day 15 and day 21, and were not taken into account for the analysis. Thirty-four questionnaires were completed at W6. The reasons for the 9 missing questionnaires were as follows: no follow-up visit at W6 ($n = 4$), use of parenteral antibiotics only ($n = 3$), late inclusion at W6 ($n = 1$), antibiotics temporarily stopped because of a severe adverse event ($n = 1$). Thirty completed questionnaires were collected at M3. The reasons for the 13 missing questionnaires were as follows: scheduled antibiotic withdrawal at W6 or between W6 and M3 ($n = 8$), no follow-up visit at month 3 ($n = 1$), no answer to phone call ($n = 1$), treatment interruption by the patient ($n = 1$), and unknown reason ($n = 2$).

At W6, 11 out of 34 patients were highly adherent to oral antibiotic therapy based on the questionnaire responses, 22 were moderately adherent and 1 was poorly adherent. At M3, 12 out of 30 patients were highly adherent, 17 were moderately adherent and 1 was poorly adherent. The questionnaire items with the lowest rate of "no" answer (answer suggesting good adherence) were items #3 ("have you already taken your antibiotics later than usual") and #6 ("do you think you have too many pills of antibiotics to take").

For all subsequent analysis, given the low proportion of patients with poor adherence, only two adherence categories were considered: high adherence (score of 6/6) and moderate/poor adherence (score of 5/6 or less).

For 21 patients, a questionnaire was available at both W6 and M3. There was no significant change in adherence to antibiotic therapy between W6 and M3 (Fig. 1).

The characteristics of patients with high and moderate/poor adherence are compared in Table 2. The only variable significantly associated with the level of adherence at W6 and M3 was the number of daily doses of antibiotic to be taken ($P = 0.04$ and 0.02 at W6 and M3, respectively): an increasing number of daily doses of antibiotic was associated with poorer adherence. In our study, 22/34 patients at W6 and 22/30 at M3 had three or more daily doses of antibiotic to be taken.

While none of the other differences between patients with high and moderate/poor adherence were statistically significant, some were suggestive. Regarding gender, a larger proportion of women was highly adherent at M3 compared with men: 7/11 versus 5/19 ($P = 0.06$), respectively. Duration of symptoms appeared to be longer in patients with high adherence compared to patients with moderate/poor adherence at W6: 1543 ± 3410 versus 249 ± 401 days, respectively

Univariate logistic regression was performed only for the continuous variable 'number of daily doses of antibiotic to take'. The probability of high adherence decreased with an increasing number of antibiotic dose intakes: OR = 0.364 [0.132–1.001], $P = 0.05$ at week 6, OR = 0.243 [0.066–0.891], $P = 0.03$ at month 3).

4. Discussion

Medication adherence is a key factor in the success of any drug therapy, as drugs basically do not work in patients who do not take them. Therefore, it is important to assess drug adherence in infectious diseases, especially when prolonged treatments are used, as adherence has been shown to decrease with time in other conditions (cardiovascular diseases, depression) [3]. While adherence has been thoroughly studied in some chronic infectious diseases such as HIV infection, little is known about adherence to antimicrobial therapy [4]. To our knowledge, this pilot study is the first to report data on adherence to antibiotic therapy in patients with BJI.

In our study, the proportion of patients highly adherent to oral antibiotics was 32% (11/34) at 6 weeks of treatment and 40% (12/30) at 3 months, as assessed by a 6-item questionnaire. The OVIVA study compared oral and intravenous therapy of BJI regarding treatment failure, treatment discontinuation, adverse events, health status and adherence to treatment. In this study, adherence to oral antibiotics was assessed by the Morisky questionnaire. A score ≥ 6 (i.e. medium to high adherence) at 6 weeks was reported in 87.6% of patients [17]. While the difference between these respective rates is huge, the questionnaires and scoring systems were not the same. In addition, with such tools, there is no consensus about how much is enough to state that adherence is acceptable. For example, if high adherence had been defined as a score ≥ 5 or ≥ 4 in our study, the rates of adherence at 6 weeks would have been 71% and 97%, respectively. This discrepancy illustrates a limitation of questionnaires as metrics to quantify drug adherence.

Adherence to antibiotic treatment has also been evaluated in a community setting where most infectious diseases affected the respiratory system, the digestive system and the genitourinary

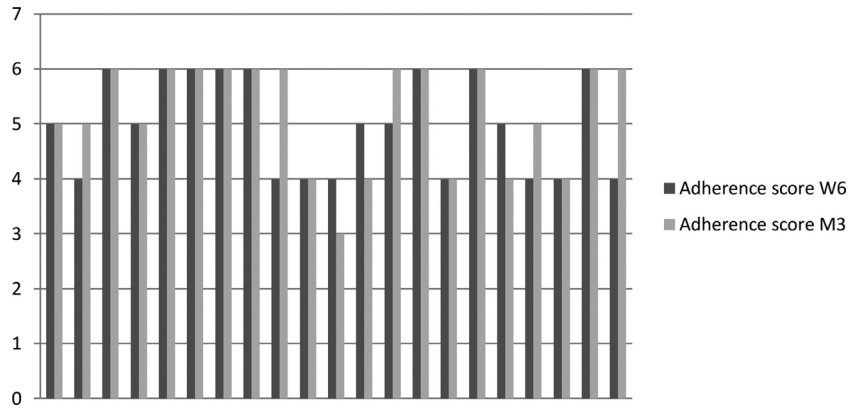

Fig. 1. Adherence score after 6 weeks (W6) and 3 months (M3) of antimicrobial therapy in each patient evaluated twice ($n = 21$).

Table 2
Influence of variables on the level of adherence evaluated by statistical comparison of highly adherent and moderately/poorly adherent groups.

Variable	Visit Week 6			Visit Month 3		
	Highly adherent	Moderately/poorly adherent	*P*-value	Highly adherent	Moderately/poorly adherent	*P*-value
Number of patients	11	23		12	18	
Age (years)	62 ± 14	60 ± 15	*P* = 0.56	64 ± 16	61 ± 13	*P* = 0.45
Men	7	16	*P* = 1	5	14	*P* = 0.06
Women	4	7		7	4	
Level of education						
< Baccalaureate	6	11	*P* = 1	4	9	*P* = 0.47
≥ Baccalaureate	5	12		8	9	
Place of care						
Home	3	13	*P* = 0.15	7	9	*P* = 0.72
Institution	8	10		5	9	
Family status						
Single	2	10	*P* = 0.25	3	4	*P* = 1
Couple	9	13		9	14	
ASA score	2.1 ± 0.6	1.9 ± 0.7	*P* = 0.45	2.0 ± 0.6	2.0 ± 0.6	*P* = 1
1	1	6	*P* = 0.40	2	3	*P* = 1
> 1	9	17		9	15	
BJI associated with medical device						
Yes	7	20	*P* = 0.18	9	15	*P* = 0.66
No	4	3		3	3	
Number of usual medications	4.4 ± 3.4	3.4 ± 3.0	*P* = 0.55	3.3 ± 3.0	4.6 ± 3.2	*P* = 0.30
< 5	6	17	*P* = 0.43	9	8	*P* = 0.14
≥ 5	5	6		3	10	
Number of oral antibiotics	1.3 ± 0.5	1.6 ± 0.5	*P* = 0.12	1.3 ± 0.5	1.5 ± 0.5	*P* = 0.19
1	8	10	*P* = 0.15	9	9	*P* = 0.26
> 1	3	13		3	9	
Parenteral antibiotics						
Yes	6	10	*P* = 0.72	2	2	*P* = 1
No	5	13		10	16	
Length of antibiotic treatment (days)	60 ± 32	47 ± 16	*P* = 0.53	92 ± 33	80 ± 28	*P* = 0.48
Number of daily doses of antibiotic to be taken	2.3 ± 0.7	3 ± 0.9	*P* = 0.04	2.5 ± 0.7	3.2 ± 0.8	*P* = 0.02
≤ 2	6	6	*P* = 0.14	5	3	*P* = 0.21
> 2	5	17		7	15	
Duration of symptoms (days)	1543 ± 3410	249 ± 401	*P* = 0.06	1280 ± 3118	362 ± 446	*P* = 0.75
Adverse events caused by antibiotics						
Yes	5	8	*P* = 0.71	1	4	*P* = 0.62
No	6	15		11	14	

Continuous variables are presented as their mean ± SD.

tract, while average duration of antibiotic treatment was 8 days. In this study, a 5-item Morisky scale exhibited a proportion of highly adherent patients of 55.2% [18]. A potential explanation for the different level of adherence is the shorter duration of treatment, especially since this work showed that increased duration of treatment was associated with higher risk of non-adherence [18].

Since drug adherence in chronic diseases is known to decrease over time, we also wished to assess the evolution of adherence during treatment [19,20]. The ability to maintain adherence to drug therapy over time is called persistence. We did not find a significant change in level of adherence between week 6 and month 3. Adherence to antibiotic therapy appeared to be stable up to 3 months.

This duration, while quite long compared to that of most common infectious diseases, is probably not a barrier to adherence, even though further research is necessary to confirm our results. However, persistence might be an issue for more prolonged BJI antibiotic therapy, as is the case for tuberculosis treatment [21]. That much said, it is difficult to extrapolate from adherence data on tuberculosis therapy, given the fact that special intervention programs have been developed in this setting, including directly observed therapy.

Factors influencing adherence have been widely evaluated in various clinical conditions and therapies, but not in BJI. In our study, the only variable significantly associated with adherence was the number of daily dose intakes. The reliability of this association is limited by the small sample size and potential confounders. However, an association between adherence and the total number of daily drug doses has indeed been demonstrated in various studies [5,22,23]. Reducing the number of daily doses was shown to be effective in increasing adherence and appeared to be more effective than minimizing the total number of medications [3]. This means that, whenever possible, in order to optimize drug adherence clinicians should prescribe a dosage regimen that minimizes the number of antibiotic dose intakes.

In this pilot study, we could not thoroughly assess other factors that might influence drug adherence. Food restrictions such as the need to take drugs on an empty stomach have been shown to influence adherence in HIV chronic treatment [24]. Rifampicin, a common agent in BJI therapy, should be taken during fasting state, and this influences the level of adherence. Other influencing factors reported in the literature include medication side effects, patients' beliefs and motivations, and patient-prescriber relationship [11,15]. In the present study, the reported frequency of side effects was probably too low to show an impact on adherence, and factors related to patient behavior were not evaluated. Lastly, the influence of some variables such as gender, age, educational level, disease factors (disease severity or fluctuation of symptoms) has varied across studies, and was not identified in the present work [11].

Our study has several limitations. First, self-reported adherence may be affected by social desirability and recall bias, and is known to overestimate true adherence [25,26]. Questionnaires provide adherence information at a given time and not for the whole duration of treatment. There are two main types of methods for measuring adherence [15]: direct methods (e.g. directly observed therapy, measurement of drug concentration or a biological marker in blood) and indirect methods including pill counts, patient self-reports, questionnaires, rates of prescription refills, medication electronic monitoring systems (MEMS®), patient diaries, and assessment of patients' clinical responses. Each method has its strengths and limitations, and no method is considered as a gold standard [15,27]. However, MEMS® are especially attractive insofar as they can provide quantitative and exhaustive data on drug intakes over lengthy observation times. They can identify special adherence patterns such as drug holidays and may also be used to improve drug adherence by providing patients with dose counts or recall.

In this non-interventional pilot study, evaluation of adherence with a questionnaire was chosen because it is easy to use, quick to perform, noninvasive and inexpensive. In a routine clinical setting, self-reported adherence measures are usually the most useful and practical methods. They can provide real-time feedback regarding adherence behavior and potential reasons for poor adherence (including social, situational and behavioral factors affecting adherence). Besides, they exhibit acceptable agreement with direct methods such as MEMS® [25]. The questionnaire by Girerd et al. was used because it did not require translation and the items could be generalized to any class of medication. Moreover, this method is recommended by French Health Insurance to evaluate medication adherence [28]. A comparison of adherence data from this questionnaire and those from MEMS would be of interest for patients with BJI.

A second limitation was the small sample size, which precludes strong conclusions, especially regarding factors influencing adherence to antibiotics in BJI. A larger study is required to clarify this question. There is a dearth of data on drug adherence in patients with BJI. The aim of this pilot work was to get a snapshot of patient adherence before carrying out a larger study in this type of clinical situation.

5. Conclusion

In this pilot study performed in patients with BJI, adherence to antibiotic therapy as estimated by a questionnaire was variable between patients but appeared to be stable from 6 weeks to 3 months. A high number of antibiotic dose intakes seemed to be a barrier to drug adherence. These findings need to be confirmed in future large-scale studies using the same questionnaire and MEMS® caps.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments

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Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

CB, EM, TF and SG participated in study design. LL and CB performed patient interviews, collected clinical data and performed statistical analysis. LL drafted the article. EM critically reviewed the manuscript draft. TF participated in data collection as the principal investigator of the study and critically reviewed the manuscript draft. SG performed statistical analysis and drafted the article. All authors read and approved the final version of the article.

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Appendix A.

1	Ce matin, avez-vous oublié de prendre votre/vos antibiotique(s)? *Have you forgotten to take your antibiotics this morning?*	☐ oui ☐ non ☐ *yes* ☐ *no*
2	Depuis la dernière consultation, avez-vous été en panne de votre/vos antibiotique(s)? *Since your last medical visit, have you run out of your antibiotic(s)?*	☐ oui ☐ non ☐ *yes* ☐ *no*
3	Vous est-il arrivé de prendre votre/vos antibiotique(s) avec retard par rapport à l'heure habituelle? *Have you already taken your antibiotic(s) later than usual?*	☐ oui ☐ non ☐ *yes* ☐ *no*
4	Vous est-il arrivé de ne pas prendre votre/vos antibiotique(s) parce que, certains jours, votre mémoire vous fait défaut? *Have you already forgotten to take your antibiotic(s) because, some days, you had difficulty remembering it?*	☐ oui ☐ non ☐ *yes* ☐ *no*
5	Vous est-il arrivé de ne pas prendre votre/vos antibiotique(s) parce que, certains jours, vous avez l'impression que votre/vos antibiotique(s) vous fait/font plus de mal que de bien? *Have you already stopped taking your antibiotic(s) because some days, you had the impression they caused you more harm than good?*	☐ oui ☐ non ☐ *yes* ☐ *no*
6	Pensez-vous que vous avez trop de comprimés d'antibiotiques à prendre? *Do you think you have too many pills of antibiotics to take?*	☐ oui ☐ non ☐ *yes* ☐ *no*

6 "no" answers: highly adherent patient; 4 or 5 "no" answers: moderately adherent patient; 3 "no" answers or less: poorly adherent patient.

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