NEW TREATMENT STRATEGIES IN HIV/AIDS INFECTION AND THE IMPACT OF TREATMENT ADHERENCE ON THE QUALITY OF LIFE OF PEOPLE LIVING WITH HIV

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SUMMARY

Objective: The aim of the study was the assessment of adherence to antiretroviral (ARV) treatment in a population of people living with HIV (PWH), improving the awareness of PWH, drawing attention to the risk of developing HIV drug resistance and subsequent treatment failure.

Methods: The basic cohort consisted of PWH followed up long-term at the HIV centre of the University Hospital Pilsen. Adherence to treatment was assessed by ARV levels. Nucleoside analogs were determined in urine by high pressure liquid chromatography (HPLC), in relation to clinical data, viral load (HIV RNA), and absolute CD4 and CD8 T cell counts. To assess mental and physical state of the patients, a modified SF-36 questionnaire was used to measure social relationships, education and ability to relax.

Results: From a group of 131 PWH, 18 (13.7%) with zero levels and 113 (86.3%) with any detectable ARV levels were followed for 6–12 months. A statistically significant lower viral load was demonstrated in patients who adhered to the treatment at the time of the test as indicated by ARV levels in the urine. CD4 T lymphocyte values in adherent patients were, as expected, statistically significantly higher. A significant difference for CD8 T lymphocyte was not demonstrated. A survey assessed subjective factors influencing the degree of adherence. PWH consider important: quality care enabling trust, low risk of developing opportunistic infections, self-sufficiency, quality of sleep, managing leisure activities, and good family relationships. Quality of life evaluation and satisfaction in the monitored areas were similar in both groups of PWH.

Conclusions: Non-adherence leads to deterioration of CD4 and viral load levels and may be the cause of the development of HIV drug resistance and treatment failure on the part of the patient. PWH with zero or low urinary nucleoside levels were repeatedly instructed about the need for regular and sustained medication use. Regular checks with a laboratory examination service are needed to detect early emergence of resistance and side effects of the treatment, which are initially only detectable in the laboratory.

Key words: adherence, antiretroviral drugs, AIDS, HIV, prevention, virus

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INTRODUCTION

It has been more than 40 years since the acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) changed the world. HIV/AIDS treatment has improved a lot since then, but it is still impossible to completely cure people living with HIV (PWH). The goal is to achieve suppression of HIV replication, e.g., the maximal elimination of concentration of HIV RNA in the blood of infected persons (1). Patient's adherence to treatment plays a key role in this process, but it is essential to start treatment with double or triple combinations of antiretroviral drugs (ARV) early (2–4). Compared to previous years, the vast majority of PWH are followed up as outpatients.

The aim of our study was to assess the adherence to antiretroviral (ARV) treatment in a population of PWH, to improve the awareness of adherence in PWH, and draw attention to the risk of developing HIV-drug resistance with subsequent treatment failure. To objectify and monitor adherence, we used a method developed by us, evaluating the presence of selected nucleosides in the urine of PWH treated with ARVs. Laboratory data were compared with data obtained from questionnaires that focused on ARV treatment tolerance, adherence and quality of life.

MATERIALS AND METHODS

The study cohort consisted of PWH that were followed up for a long time in the HIV centre of the University Hospital Pilsen. The study was designed as prospective, controlled, and open.

The initial selection of suspiciously non-adherent PWH was carried out by asking as part of a routine planned follow-up, or according to previous laboratory findings, showing fluctuations in HIV RNA viral load (VL) levels, or even a decrease in the number of CD4 T lymphocytes. PWH were enrolled continuously based on detected clinical and laboratory indications of non-adherence. The definitive division into groups of truly non-adherent PWH and adherent PWH on the given day of the examination was performed only after the detection of a negative level of NTRI in the urine. Investigation of the ARV adherence status was conducted continuously for all PWH at each follow-up visit.

In the study PWH who either admitted to insufficient adherence or had repeatedly demonstrated a decrease in CD4 T lymphocytes, or a worsening of virologic findings compared to the previous check-up, were included. In 148 patients, 404 urine tests for the presence of nucleoside reverse transcriptase inhibitors (NRTI), azidothymidine (AZT), lamivudine (3TC), or emtricitabine (FTC), depending on the type of used ARV combination were performed. Urine was sampled 2–6 hours after taking the morning dose of medication. Each person underwent 1 to 11 examinations as required during the reporting period. The values of viral load, CD4 and CD8 T lymphocytes were subsequently compared on the day of the determination of the drug in urine, and at the previous, and also the subsequent check-up, i.e., 3–6 months earlier, and 3–6 months later.

The levels of 3TC, FTC and AZT, using the HPLC device (Spectra Physics, San Jose, CA, USA), were determined. The principles of the NRTI detection by HPLC had been described elsewhere (5). The HIV RNA PCR investigation took place at the National Reference Laboratory (NRL) for HIV/AIDS in Prague. The viral load was quantified using the instrument Cobas 4800 (Hoffmann-La Roche, Basel, Switzerland). Determination of lymphocyte subpopulations using a flow cytometer (FACS) Navios (Beckman Coulter, Brea, CA, USA) was performed in the Institute of Immunology and Allergology of the University Hospital in Pilsen. A modified RAND 36 – Item Health Survey (SF-36) questionnaire was used for the subjective evaluation of antiretroviral treatment and adherence by the patients themselves. Individual subjective answers were evaluated by patients on a point scale of 0–5 points (0 – least matched, 5 – the most matched).

Data analysis was performed using the Stata statistical software, release 17 (Stata Corp LLC, College Station, Texas, USA). The values of laboratory markers (VL, CD4 and CD8 T lymphocytes) are characterized by median and interquartile range (IQR) and compared between groups by Mann-Whitney test. Median regression was used to test whether there were changes in marker values at the three time points. Items from the quality-of-life questionnaire were compared between groups by the two-sample t-test based on means. Test results with p-values less than 0.05 were considered statistically significant. Graphs were generated using Excel SW (Microsoft, USA) and Stata software.

The study was approved by the Institutional Review Board and Local Ethics Committee of the Medical Faculty in Pilsen, Charles University, and University Hospital in Pilsen on 7 January 2021 (approval number EK-07012021/5), and it complies with the Declaration of Helsinki and local laws. All patients' data was anonymized.

RESULTS

During the period of 2010–2020, a total of 151 PWH from the HIV Centre of the University Hospital in Pilsen were selected for the purposes of our study. Three patients were excluded based on exclusion criteria, and 17 PWH were excluded because an inappropriate urine nucleoside test was mistakenly ordered. The PWH's level of education was analysed and found to be consistent with the overall distribution of the population of the Czech Republic (Table 1) (6).

Finally, 377 urine samples, acquired from 131 PWH, were tested for the presence of NRTI. In 357 urine samples, obtained from 113 patients, the monitored drug was detected, therefore, these patients were evaluated as adherent to the treatment even though viral load (HIV-1 RNA) and CD4 T lymphocytes were detected. Concentrations of the monitored substances in the urine ranged from 0.2 to 1840.6 mg/L. In 20 samples obtained from 18 PWH, the expected drug or its metabolite (1x AZT, 13x FTC and 6x 3TC) were not detected in urine. These patients were evaluated as non-adherent on the day the examination was performed. After the evaluation of laboratory data and the survey, the patients were divided into two groups: adherent and truly non-adherent. The patient data is displayed in Table 2. The proportion of positive urine samples among all the samples analysed was 94.7%, but the adherence, calculated as a ratio of the adherent PWH to the whole group of PWH, was only 86.3%.

As shown in Table 3, statistically significant differences between the adherent and non-adherent groups were found for CD4 T lymphocytes (lower values in the non-adherent group) (Fig. 1) and VL (higher values in the non-adherent group) at all the three time points evaluated. For VL, this is a highly significant difference, although it is not apparent from the median at first glance. However, IQRs differ substantially, indicating a large range of values in the non-adherent patients. There are no statistically significant differences in CD8 T lymphocytes and the CD4/CD8 ratio between the groups. As documented by p-values from the median regression in Table 3, changes over time (for the three

Table 1. *Achieved education of PWH in the survey compared to Czech Republic inhabitants*

Achieved education	Population of the Czech Republic (%)	PWH included in the survey (%)
Unfinished elementary	0.1	0.0
Elementary	16.3	16.3
Secondary without maturity	35.2	39.5
Secondary with maturity	33.7	30.2
University	14.6	14.0

Source: Code list (6)

Table 2. *Description of the cohort of adherent and non-adherent PWH*

Evaluation	Patients count	Urine samples	Notes
Total of PWH recruited	151		
Excluded	3		Based on exclusion criteria
All PWH tested	148	404	
Wrong test requested	17	27	Excluded from the study
PWH correctly included	131	377	
Adherent PWH	113	357	Total adherence 86.3%
Non-adherent PWH	18	20	Non-adherence 13.7%

In 18 PWH neither the drug nor its metabolite was detected in urine. These patients were evaluated as non-adherent on the day the examination was performed.

monitored measurements) are not statistically significant for any marker in any group.

The assessment of PWH's adherence to treatment also included answering questions in a questionnaire. In addition to demographic data, the simplified SF-36 questionnaire also contained 23 questions assessing selected facets of the quality of life that PWH rated on a scale from 0 to 5. A total of 43 (33%) questionnaires were processed and returned by the patients (34 from adherent and 9 from non-adherent PWH). The arithmetic means of the ratings of the monitored items are shown in Figure 2. The differences between the groups are not large, yet some are noticeable: the adherent PWH prefer politics, truth, sexual life, hobbies in free time, love, and raising children. The non-adherent PWH highlight health, justice, religion, work, psychological well-being, good sleep, feeling of safety, art, family relationships, and physical self-sufficiency. However, the differences between these groups are not statistically significant in any of the questions ($p > 0.05$).

Table 3. *Comparison of laboratory markers between the cohorts of adherent and non-adherent PWH*

Characteristic	Cohort		p-value[a]
	Adherent (n = 113) Median (IQR)	Non-adherent (n = 18) Median (IQR)	
CD4 T lymphocytes			
Time −3	660 (390)	470 (470)	0.030
Time 0	740 (440)	515 (440)	0.005
Time +3	720 (430)	540 (430)	0.013
p-value[b]	0.067	0.065	
CD8 T lymphocytes			
Time −3	785 (470)	740 (620)	0.630
Time 0	780 (430)	670 (300)	0.140
Time +3	790 (490)	785 (420)	0.673
p-value[b]	0.617	0.148	
CD4/CD8 ratio			
Time −3	0.81 (0.74)	0.67 (0.79)	0.175
Time 0	0.88 (0.78)	0.85 (0.96)	0.271
Time +3	0.90 (0.78)	0.68 (0.94)	0.037
p-value[b]	0.104	0.496	
Viral load			
Time −3	0 (20)	38 (1011)	< 0.001
Time 0	0 (20)	20 (1801)	< 0.001
Time +3	0 (20)	20 (201)	< 0.001
p-value[b]	0.076	0.874	

IQR – interquartile range; time 0 indicates the day on which the nucleoside levels in the urine sample were tested; time −3 means results obtained 3 months earlier; time +3 means results obtained 3 months after; [a]p-value for comparison of groups; [b]p-value for assessment of changes over time within a group

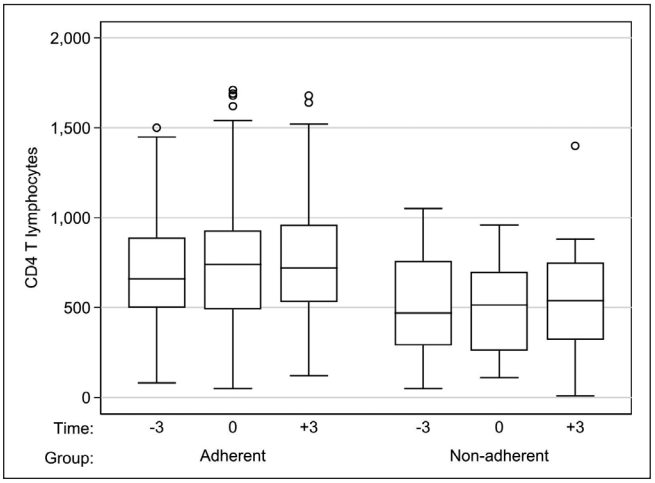

Fig. 1. *Distribution of CD4 T cell counts in the adherent and non-adherent groups on the day of urine nucleoside levels testing (time 0) and three months before (time −3) and three months after the collection (time +3).*

DISCUSSION

The aim of this article has been to point out new trends and possibilities of treatment and treatment strategies of HIV/AIDS with focus on treatment adherence. The trend in recent years has been to maximize the effectiveness of HIV treatment and to optimize the tolerance of the treatment by patients. If complete therapy in PWH is simple and acceptable, it is better tolerated and controlled, so the overall adherence should increase. At the same time, the overall adherence can be relatively easily checked, for example by monitoring the levels of therapeutic substances in the patient's blood and urine, or in the dried breast milk spots (7), or even in hair (8).

In our study we have used an original method of detection of NRTI in urine to monitor the adherence status in PWH. Other similar methods testing the blood levels of various ARV have been described (9–11). Our method for the evaluation of adherence to antiretroviral treatment is simple, safe and very effective.

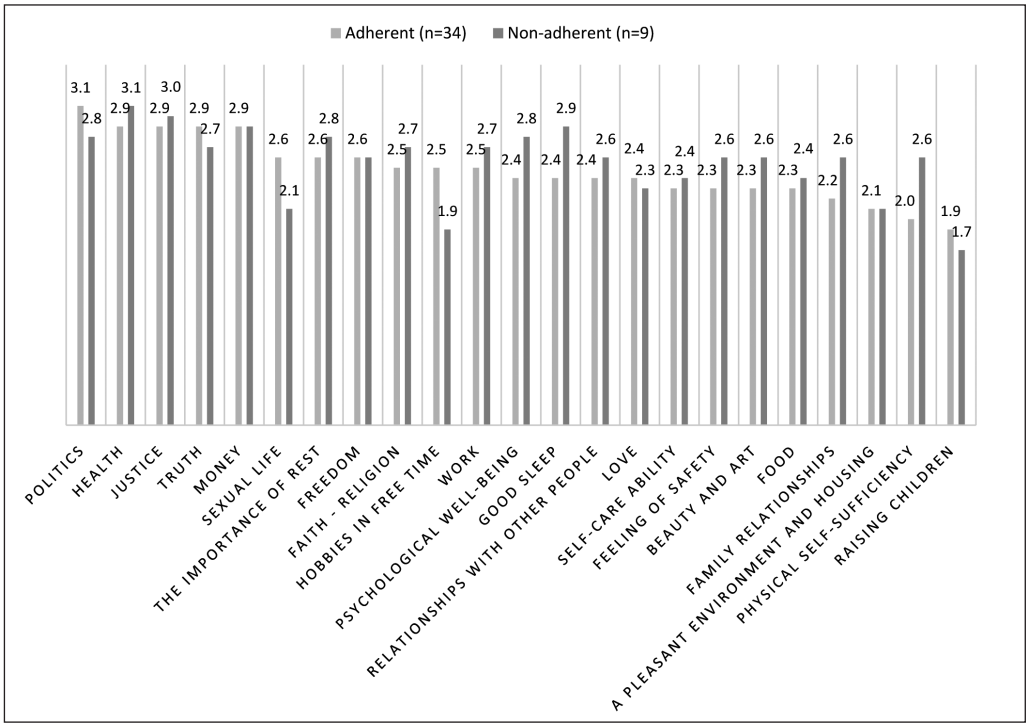

Fig. 2. *Subjective evaluation of quality of life by adherent and non-adherent PWH in the survey.*

For 23 questions, the average scores in the groups are given. The difference between the two groups is not statistically significant in any of the questions.

However, we found only a few reports on the determination of ARV in urine (12–15), all published much later than our original communication (5).

The term adherence/non-adherence is defined here based on the level of the drug on a given day and it may not fully correspond to the common understanding of adherence measured by VL.

In the adherent PWHs, significantly higher CD4 counts were demonstrated compared to the non-adherent group (Fig. 1). On the other hand, significantly higher VL was shown in the group of nonadherent PWHs. However, we are aware that in the long term, the level of NRTI in the urine of an adherent patient may be undetectable on the day of the examination for various reasons and vice versa.

For this reason, we are newly introducing repeated random urine testing for the presence of NRTIs in PWHs where the numbers of dispensed and consumed tablets of the drug do not agree during individual check-ups, as well as in persons in whom blips have been repeatedly detected, and in PWH, where CD4 counts decrease over time.

Only repeatedly proven undetectable levels of NRTI in urine, together with findings of higher VL in the longer term, can explain true nonadherence, which can lead to the development of HIV resistance and eventually to ARV failure.

An occasional persistent problem, closely connected with the quality of life, that unfortunately affects PWH is a persisting stigma. Stigmatization often leads to PWH disadvantage in the community and thus in many cases causes psychological problems, leading to lower quality of life. Long-term stress, exhaustion and sometimes also existential problems may be reflected in worse PWH adherence (16, 17). PWH complain that it is still very difficult to find, for example, dental, but also other health care. We were also interested in whether the perception of social, personality and relationship issues can be reflected in the acceptance of the rules of adherence.

The results of the survey confirmed that the magnitude of values, as well as relationships to some life situations, are sometimes different for the non-adherent PWH (Fig. 2). We wondered if other authors had encountered similar results. International studies show that even today the adherence to antiretroviral therapy is still not ideal in some countries. A study of the Houston Health Services Research and Development Center of Excellence shows that adherence to HIV/AIDS treatment and quality of life is dependent on patients' self-monitoring. If self-monitoring is regularly carried out, e.g., patients are regularly invited to screening and are both educated and checked for using drugs, treatment adherence is approximately 95% (18). This figure is better when compared with the results of the investigation carried out at the Department of Infectious Diseases and Travel Medicine of Faculty Hospital in Pilsen (17, 19). Monitoring and evaluating adherence to treatment and other medical care has proven to be indispensable, both for health and economic reasons. This is the only way to ensure that the financial resources as well as human resources are used efficiently throughout the whole health system, not only when working with HIV-positive patients (17). In addition, the use of all new antiretrovirals which are available today ensures that the overall treatment regimen will be the most effective for patients and thus clearly beneficial and with positive impact on their quality of life.

Research focusing on the quality of life of PWH and the adherence to their treatment carried out in 2014 and later at our department showed that PWH's social conditions affect the subjective perception of the quality of their life. From the specific indicators which were monitored, this was especially true about the financial situation and material security. This implies that if PWH are disadvantaged when applying for a job because of

being HIV-positive, this will impact the quality of their lives, even if they adhere to their treatment. Conversely education, partnerships/marriage, as well as other monitored factors, do not substantially affect the subjective perception PWH's quality of life. Also some differences were found in the subjective perception of the quality of life of non-adherent and adherent PWH. This could suggest relation between the quality of life and PWH's adherence to treatment. PWH's psychological well-being was better prior to their diagnosis of HIV infection than during treatment, despite its maximal possible quality and availability (19). The minimization of risks associated with the occurrence of opportunistic infections and their prevention also has a direct effect on the degree of adherence.

Strengths and Limitations

The strength of the study is in the precise measurement of NRTI levels in urine using a very sensitive method, objectively demonstrating adherence to ARV in the investigated PWH. It turned out that in cases where non-adherence was considered, it was objectified only in 13.7% of the cases. The potential limitation of the study concerns situations that involve a short-term omission of medication intake, resulting in a detection of a negative level of NRTI in urine, but with HIV RNA and total CD4 T lymphocyte counts unchanged in the long term. Another limitation concerns the questionnaire, where the individual questions can be evaluated and answered completely differently by subjects under different external or internal circumstances. Moreover, in the non-adherent group questionnaire observations were of low number.

CONCLUSIONS

HIV infection is still incurable, and its course and duration depend on many factors. It has been repeatedly proven that the correct selection of specific drugs and a high degree of PWH adherence significantly influence the course and prognosis of the disease. The minimum adherence that ensures optimal results of antiretroviral therapy was determined to be 95% many years ago. Although the patients in our cohort did not achieve such a high degree of adherence, after explaining the need to take medication regularly and to attend scheduled check-ups, we observed an improvement in somatic, psychological and laboratory indicators in the majority of PWH.

Non-adherence leads to deterioration of CD4 and VL levels and may be the cause of the development of HIV drug resistance and treatment failure on the part of the patient. PWH with zero or low urinary nucleoside levels were repeatedly instructed about the need for regular and sustained medication use. Regular checks with a laboratory examination service are needed to detect early emergence of resistance and side effects of the treatment, which are initially only detectable in the laboratory.

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Conflicts of Interest

None declared

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