Progetto (C.A.R.E.): "Gestione assistenziale di pazienti HIV positivi in soppressione virologica: ricerca e valutazione di un nuovo paradigma di cura.

"Continuum Assistance of virally suppressed HIV-positive patients: Research and Evaluation of new paradigms of care" (C.A.R.E.) project. Retention in care and quality of life in virologically suppressed HIV-population.

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Riassunto

È stato proposto di aggiungere un "quarto 90" agli obiettivi di diagnosi e cura per le persone affette da infezione da HIV, per garantire che il 90% delle persone con soppressione della carica virale abbia anche una buona qualità di vita. Questo nuovo obiettivo amplierebbe il paradigma del continuum dell'assistenza, oltre l'*endpoint* già esistente della soppressione virale, utilizzando gli strumenti disponibili per rilevare la condizione di disagio correlata ad un'infezione cronica. Appare necessario prendere in considerazione le comorbidità e la qualità della vita auto-percepita per la valutazione della qualità della vita nelle persone con HIV, realizzando un nuovo approccio a questo argomento ancora non ben approfondito. Lo scopo dello studio è stato quello di valutare negli adulti positivi HIV stabilmente viro-soppressi il grado di aderenza e di compliance alla terapia, la qualità della vita auto-percepita e la presenza di comorbidità, al fine di identificare eventuali eventi sentinella precoci, che influenzano l'aderenza del paziente, e pianificare approcci personalizzati al fine di migliorare l'aderenza per quei pazienti con un rischio di ridotta compliance terapeutica. Nel complesso, la qualità della vita auto-percepita nel nostro studio era buona. Più precisamente, il 70% degli intervistati ha posto il proprio stato di benessere nel punteggio compreso tra 70 e 100 e il 20% tra 40 e 50.

Abstract

It has been proposed to add a "fourth 90" to the testing and treatment targets for people living with HIV, to ensure that 90 % of people with viral load suppression have also good quality of life. This new target would expand the continuum of services paradigm beyond the existing endpoint of viral suppression, using available tools to detect the discomfort of a chronicity. Co-morbidities and self-perceived quality of life need to be considered for evaluation of quality of life in people with HIV, realizing a novel approach to this largely underestimated topic. In HIV stably virologically suppressed positive adults, we evaluated the degree of adherence and therapeutic compliance, the self-perceived quality of life and the presence of co-morbidities, in order to identify any early sentinel event affecting patient's adherence, to plan personalized tailored approaches, to support and improve adherence for patient at risk of reduced compliance to the treatment. Overall, in our setting the self-perceived quality of life of patients was good. More specifically, 70% of the respondents placed their state of well-being on the score between 70 and 100 and 20% between 40 and 50. Only three patients declared themselves not satisfied with their psychophysical condition, identifying it with scores between 30 to

Solo tre pazienti si sono dichiarati insoddisfatti della propria condizione psicofisica, identificandola con punteggi compresi tra 30 e 40 in due casi e tra 10 e 20 in un caso. La maggior parte dei pazienti ha riportato anche una condizione di benessere ed equilibrio più che accettabile, con un'incidenza di sintomi molto bassa (soprattutto stanchezza), che non ha influenzato le normali attività della vita quotidiana. I risultati del nostro studio, anche se non significativi per l'adozione di un approccio psicoterapeutico di massa, hanno comunque consentito l'avvio precoce di un percorso psicoterapeutico personalizzato per migliorare l'aderenza e gestire la depressione. In conclusione, la valutazione soggettiva della qualità della vita, della depressione e di altri eventi sentinella può diventare una variabile molto importante per l'implementazione dei programmi di assistenza medica, al fine di migliorare l'aderenza ai percorsi di terapia e prevenzione e di ottenere un soddisfacente livello di interazione con l'operatore sanitario. Pertanto, si ritiene essenziale includere questo tipo di valutazione nella pratica clinica di routine. Il questionario a risposta multipla è uno strumento pratico, semplice ed affidabile per rilevare precocemente eventuali barriere all'aderenza terapeutica al fine di prevenire il fallimento virologico e salvare future opzioni terapeutiche.

40 in two cases and between 10 and 20 in one case. The majority of patients also reported a more than acceptable condition of well-being and balance, with a very low incidence of symptoms (mostly fatigue), that did not affect the normal daily life activities. The results of our study, even if not significant for the implementation of mass psychotherapeutic approach, however allowed the early start of a personalized psychotherapeutic pathway to improve adherence and manage depression. In conclusion, subjective assessment of the quality of life, depression and others sentinel events can become an especially important variable for the implementation of clinical care programs, to improve adherence to therapy and prevention protocols and to obtain a satisfactory level of interaction with the healthcare professional. Therefore, we consider essential to include this kind of assessment in routine clinical practice. The multiple response questionnaire is a practical, simple, and reliable instrument to early detect eventual barriers to therapeutic adherence, in order to prevent virological failure and to save future therapeutic options.

Background

A new Global Health Sector Strategy on HIV from World Health Organization (WHO), with the aim *"to end the AIDS epidemic as a public health threat by 2030"*, establishes 15 ambitious targets for 2016-2021, including the "90-90-90" target in order to reduce under-diagnosis, treat a greater number of those diagnosed, and to ensure that those treated achieve viral Human Immunodeficiency Virus (HIV) suppression (1-3). The three 90th targets represent a new mindset to manage HIV epidemy, but there is still another very important goal to achieve, that is to ensure healthy life and promoting well-being in people living with HIV (PLHIV).

Data on the "third 90" show in almost all the European cohorts, including the Italian one, that the "third 90" of effectively treated patients has been widely reached up.

However, HIV management includes also dealing with some psychosocial variables such as anxiety and depression, stress, fear of transmitting HIV to others, uncertainty about the future, and social stigma. These issues have a strong impact in Quality of life (QoL) of PLHIV. Drawing from this background, it has been proposed to add a "fourth 90" to the testing and treatment targets to ensure that 90 % of people with viral load suppression have also good QoL. This new target would expand the continuum of services paradigm beyond the existing endpoint of viral suppression using tools available to detect the discomfort of a chronicity. Co-morbidities and self-perceived quality of life need to be considered for QoL HIV evaluation (3), realizing a novel approach to this largely underestimated topic (4-5).

PLHIVs have high risk for non-HIV-specific diseases such as kidney disease, cardiovascular disease, and various cancers, due to the persistence of a state of immune activation and inflammation, despite effective antiretroviral therapy (ART) (6-9). Today, the prevalence of non-HIV related co-morbidities is increasing and more than 50% of PLHIVs are multi-morbid and about 30% have three or more concurrent co-morbidities (9).

As for self-perceived quality of life, virally suppressed PLHIVs frequently reported high levels of symptoms such as fatigue and energy loss, insomnia, sadness and depression, sexual dysfunction, and changes in body appearance. An important variable to consider is how much these factors affect the quality of life and adherence to treatment. In particular, depression is the most common neuropsychiatric complication in HIV-infected patients, and it may occur in all phases of

the infection. Rate of depression is high in women with HIV and a common cause of poor adherence to treatment in PLHIVs (10-15). Therefore, it is extremely relevant to evaluate quality of life, depression, and other sentinel events also, in virally suppressed PLHIVs, in order to highlight any reductions of adherence to therapy levels. An easy-to-use tool is the self-reported adherence questionnaires, that seems a surprisingly accurate instrument to measure ART adherence and can be reliably used in resource-poor settings.

Aims of the study.
1. To evaluate in stably viro-suppressed HIV positive adults the degree of adherence and therapeutic compliance, the self-perceived quality of life and the presence of co-morbidities.

2. To early identify any sentinel event with an impact on adherence.

3. To plan personalized tailored approaches to support and improve adherence in patient at risk of reduced compliance to the treatment.

Material and methods
A multiple response questionnaire was offered from June 2018 to January 2020 to PLHIVs observed at the "D. Cotugno" Hospital of Naples, to obtain data about the aims of the project.
Inclusion criteria were: adult patients, availability to sign informed consent, HIV infection, stable virosuppression (HIV RNA <50 cp/ml) for more than 96 weeks on antiretroviral therapy.
Sixty-five adult subjects (25 females and 40 males) met the inclusion criteria and were enrolled in the study.
All patients but four were Italian. All foreign patients included in the study were permanently resident in Italy, perfectly integrated and able to speak the Italian language, in order to facilitate the interpretation of the questions included in the questionnaire and to provide answers as reliable as possible.
The average age of the sample was 45.4 years (range 37-70 years) with no significant differences between female and male. All patients were in ART from at least two years and had viral load values steadily lower than 50 copies/ml (measured with real time

PCR, Roche COBAS 6800) for at least 9 months. Mean count of CD4 cell count was >250 cells/mcL.
All patients provided a signed informed consent.
Questionnaire was characterized by a multidimensional structure to evaluate several variables related to each other and all of them related to adherence to therapy and quality of life. After the first part dedicated to the collection of socio-demographic data, the questionnaire proposed a series of questions relating to ART, the presence of one or more co-morbidity and adherence to ART and non-ART therapies. Adherence to treatment and the impact of HIV on QoL were investigated using the ISSQol Questionnaire by Bucciardini et al. (16). Overall, the questionnaire consisted of 17 areas QoL related **(Table 1)**.

Results
Ten out of the 65 patients had an elementary school diploma, 15 had a middle/lower school diploma and 30 a middle/high school diploma. Ten patients were graduated and four of them had also a specialization diploma or a post-graduate master's degree. Forty-nine patients reported permanent job and 10 were unemployed, while six benefited from a disability pension. Less than a half of the subjects (32/65) lived alone, 23 lived with a partner and ten lived in their parents' house or with the family of a brother and/or sister.

Therapies and self-reported adherence
Nine out of 65 patients were on first line of antiretroviral treatment, the remaining (57/65) had changed one or more regimens after the ART introduction, with one of them that experienced five therapeutic changes. In all cases, therapeutic switches were due to regimen simplification or to a pro-active reduction of drug-toxicity. Fifty-six out of the 65 subjects were on ART from more than five but less than 10 years; nine out of 65 patients were on ART for more than 10 years. About 40% of the patients were anti-HCV positive, while eighteen referred co-morbidity (especially diabetes and/or hypertension) and were on polypharmacy with other than antiretroviral drug. Most of them (15/18) did not report problems for the management of the various therapies nor did they report interactions between antiretrovirals and other drugs.

Variables	Item	Type	References
Demographic data	8	Multiple choice	Ad hoc
Clinical data and adherence	13	Multiple choice	ISSQol
Quality of life	2	Likert Scale	ISSQol
Physical well-being	1	Likert scale	ISSQol
Job role well-being	1	Likert Scale	ISSQol
Social Support	1	Likert Scale	ISSQol
Social well-being	1	Likert Scale	ISSQol
Depression and anxiety	1	Likert Scale	ISSQol
Strength and vitality	1	Likert Scale	ISSQol
HIV related Psychological Stress	1	Likert Scale	ISSQol
Cognitive function	1	Likert Scale	ISSQol
Sexual behavior	2	Multiple choice and Likert Scale	ISSQol
Relationship with health care system	2	Likert Scale	Ad hoc
Treatment impact	1	Likert Scale	ISSQol
Physical change	1	Likert Scale	ISSQol
Thinking of future	1	Likert Scale	ISSQol
General Health	1	Likert Scale	ISSQol
Motherhood/Fatherhood	2	Multiple choice and Likert Scale	Ad hoc
Other somatic symptoms	1	Likert Scale	Ad hoc

Table 1. Quality of life related areas.

Adherence to therapy and compliance to ART prescription

Most patients declared to regularly take the therapy according to prescriptions.

About a quarter of them said that they "had not missed" even a dose in the last 6 months.

Forty-seven/65 subjects, although showing an overall good adherence, reported at least one skipped dose or a delay in taking the drugs in the same period. Out of these group 35/47 related it to a simple occasional forgetfulness, 19/47 motivated it with work problems and 10/47 to the difficulty of taking the tablets in relation to a meal. Only one patient reported repeated failures to take the therapy because the difficulty to accept his own illness condition and the thought of having to take drugs all along the life. In addition, it was evaluated the influence of therapeutic switches on the level of adherence to the treatment.

Thirty-four of the 57 experienced patients reported no reason to correlate the two variables (change of therapy vs. adherence). However, six of them effectively correlated the worsening of adherence to the therapeutic switch even if more compact regimens with reduced side effects (mostly single tablet regimens, STR) were prescribed.

Finally, the correlation between the appearance of a traumatic event (such as bereavements, marital separation, changes of the home or work, feeling/certainty of a worsening of one's health, etc.) and the worsening of adherence to therapy was investigated. Six subjects showed a negative correlation between job change and adherence levels, while only one patient correlated the reduced adherence to a family mourning and to the consequent depressive condition. Finally, three patients displayed a significant decrease of the adherence to therapy related to anxiety and depression.

Quality of life, Physical well-being, and Social well-being

The perception of psychophysical well-being was assessed by a progressive score ranging from 10 (to indicate lowest quality of life) to 100 (that indicates highest quality).

The overall self-reported quality of life was satisfying. More in details, 10/65 placed their state of well-being between 90 and 100, 17/65

just below, between 80 and 90, 20/65 patients between 60 and 70 and 15/65 between 40 and 50. Only three patients clearly declared themselves dissatisfied with their psychophysical condition identifying it with scores ranging around 30-40 in two cases and between 10 and 20 in one case. Most patients also reported a more than acceptable condition of well-being and mental balance, with a low incidence of symptoms (mostly fatigue), that did not interfere with the normal daily life activities. Almost all subjects reported that neither the disease nor the antiretroviral therapy had a negative influence on their life and social relationships. Regarding the influence of the disease on work activities, our patients did not report significant difficulties in the performance of their professional duties. Nevertheless, 5% of them (14/65 subjects) reported that HIV has an influence in their job choice. Finally, considering the socio-economic support, the majority of patients reported to rely on their family and close friends. On the other hand, the appeal to self-help groups and voluntary associations were considered rarely.

Depression, anxiety, vitality, and disease-related discomfort
Twenty-six out of the 65 subjects reported to have often experienced a sense of anxiety mixed with depression, mostly related to the thought of suffering from a disabling and still life-threatening disease.
Reduced physical power and vitality was reported especially among women that also reported a more or less relevant reduction in libido (and sexual interest in general), with negative impact on couple life (especially in older patients). However, when investigating the effects of the infection/disease on sexual activity in the last 4 weeks, 24/65 subjects declared themselves quite satisfied with their sexual activity and 26 were even "very satisfied". Only 15 patients were not very satisfied (12/15) or frankly dissatisfied (3/15). Patients being questioned also excluded that the ART can be a negative factor for the couple's sexual activity.
An unspecified feeling of discomfort and concern for the future, linked to uncertainty about the evolution of the disease, emerged in a relevant number of the tested subjects. A reduction in cognitive functions with short-term memory

deficits and impaired concentration was also frequently reported, mostly by women. Finally, some multi-experienced women also expressed concerns and fears about the long-term impact of therapies on changes in physical appearance, because previous treatment with drugs affected by relevant lipodystrophic impact.

Additional items
The desire for parenting was a relevant topic for most patients. The women of childbearing age reported a strong desire for motherhood without showing concern for any unwanted effects of therapy in pregnancy. A desire for paternity emerged also among males and among homosexual couples.
Finally, we observed that almost all subjects reported to be satisfied with their relationship with the medical and nursing staff of the Center, appreciating to be followed by the same doctor all over time.

Discussion
Despite substantial advances in the last decades, non- or poor adherence to ART regimens continues to be a major challenge in the real-life. The problem is ubiquitous. Successful long-term treatment of HIV/AIDS requires at least 95% adherence to ART to prevent emergence of drug-resistant HIV variants, leading to regimen failure and limited therapeutic options (17-18).
The barriers to adherence observed in HIV treatment resemble barriers to the successful treatment of other chronic diseases, that is therapeutic regimen complexity, side effects resulting in poor tolerability, patient lifestyle factors and patient-physician relationships.
There are different ways to evaluate the patient's adherence to therapies. The self-reported adherence seems a surprisingly accurate instrument for measuring ART adherence and it can be reliably used in clinical practice in limited resource settings (19-21). However, self-reported adherence is useful for identifying adherence behavior, but it needs to be matched with the clinical and laboratory data.
Overall, the levels of therapeutic adherence and compliance in our patients were satisfying. Forty-seven out of 65 subjects reported at least one dose skip or a delay in taking it in the last six

months. The match with the values of the HIV viral load and the evaluation of the regular presence of patients at the pre-established controls allowed the validation of the data on self-reported adherence.

No differences in adherence levels were then, observed in relation to gender, age, educational status and regimen complexity.

The sentinel events analysis related to reduced adherence showed some interesting aspects. One of these was the change of the therapeutic regimen, especially in the weeks following the switch. This is probably related to doubts about the efficacy and safety of the new regimen that, even if simpler to take and with low toxicity, it is considered *"as new"* by the patient. Therefore, it could be useful to switch therapy only after having adequately informed the patient about the reason, the methods of administering the new regimen, and its potential side effects, ensuring special medical counseling during the first period of new drug administration.

Another variable worth considering is the impact of traumatic events (death of a family member, such as a partner or a friend, or a job loss, a marital separation, with the consequent depressive status). Investigating these topics on a control visit will provide the physicians with information on an important variable to predict patients' adherence. This kind of variable must be included in the differential diagnostics of therapeutic failures, together with the emergency of resistance mutations, pharmacokinetic and pharmacodynamics factors, drug-drug interactions and others.

For HIV infected patients, life expectancy increase has turned this infection into a chronic disease with the resultant appearance of co-morbidities. Consequently, there is an increased burden of concomitant medication, making the HIV-infected person a poly-medicated patient (22). The prevalence of polypharmacy is high, mostly among PLHIVs ≥50 years. In our cohort, co-morbidities, interactions and drug-associated side effects were similar to those described in the literature. Polypharmacy was associated with poorer health-related outcomes among PLHIVs and medication side effects were a significant predictor of non-adherence especially among women (23-25).

More in details, co-morbidity and polypharmacy were reported in one third of our patients, even if not related to therapeutic management of HIV infection, because of the current availability of drugs with poor side effects and low level of drug-drug interactions.

The depressive disorders are one of the main indicators of reduced adherence. Depression is often difficult to recognize, especially in the early stages. HIV-positive individuals are more likely to be diagnosed with major depressive disorders than HIV-negative subjects. The diagnosis of depression in PLHIVs can be hidden by the possible effect of the physical symptoms of the infection (e.g. fatigue, decreased appetite and sleep and weight loss) and cognitive problems (e.g. slowdown, forgetfulness and difficulty concentrating). Depression can precede diagnosis and be associated with other risk factors for infection.

The experience of illness can exacerbate depressive episodes and depression can be a side effect of therapy. In an extensive review of 90 investigations, Sherr *et al.* reported a prevalence of depression reaching up to 80% of the patients studied, according to different tools and threshold scores adopted (10). Arseniou *et al.* showed that the chance of a person with HIV to have a major depression condition in accordance with international classification systems (DSM-IV or ICD-10) is up to 7 times higher than the general population (12-14). In the general population, the prevalence of depression is higher in female subjects (26-27).

Accordingly, it is estimated that HIV positive women are more likely to experience depressive symptoms compared with HIV negative women of the same age (19.4% vs. 4.8%). HIV positive hospitalized women present depression symptoms ranging from 2 to 35%, while 30 up to 60% of not hospitalized HIV positive women suffer from depression (28).

About one half of our subjects showed anxiety mixed with depression one or more times in a day, mostly related to the thought of being affected by a disabling and still potentially life-threatening disease. Lack of strength and vitality, asthenia, trend to crying were frequently reported among the women. These symptoms, sometimes hidden during a single visit, should not be underestimated in PLHIVs even in virologically suppressed patients. This phenomenon is particularly evident in the female sex, also because it usually seems inadequately investigated in the male population.

People living with HIV have significantly lower QoL than the general population, despite virological and immunological success. Factors independently associated with lower QoL were older age, HCV co-infection, co-medication in addition to ART, hospitalization due to HIV-related illness and CD4 cell count <200 cells/mm^3 (compared with CD4 cell count >500 cells/mm^3) (29).

Overall, the self-perceived quality of life in our setting of patients was good. More specifically, 70% of the respondents placed their state of well-being on the score between 70 and 100 and 20% between 40 and 50. Only three patients declared themselves not satisfied with their psychophysical condition identifying it with scores between 30 to 40 in two cases and between 10 and 20 in one case.

Most patients also reported a more than acceptable condition of well-being and balance, with a very low incidence of symptoms (mostly fatigue) that did affect the normal daily life activities. However, some biological indicators such as CD4 levels, or some global performance indexes, such as Karnofsky's, do not allow us to clearly understand some relevant aspects of PLHIV perception of their general health.

Especially in early stages of the infection, it is therefore necessary to consider the complex of emotional experience.

The results of our study, even if not significant for the implementation of mass psychotherapeutic approach, allowed the early start of personalized psychotherapeutic pathway to improve adherence and manage depression.

Conclusion

The assessment of the quality of life, depression and others sentinel events can become a relevant aspect for the implementation of clinical care programs, in order to improve adherence to therapy and prevention protocols and to obtain a satisfactory level of interaction with the healthcare professional. Therefore, we consider essential to include this kind of assessment in routine clinical practice. The multiple response questionnaire is a practical, simple and reliable instrument to early detect eventual barriers to therapeutic adherence, in order to prevent virological failure and to save future therapeutic options.

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