Articoli originali

Original articles

Integration among hospital pharmacists and infectious diseases physicians in the outpatient management of HIV infection

Integrazione tra farmacisti ospedalieri e medici infettivologi nella gestione ambulatoriale dell'infezione da HIV

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INTRODUCTION

Antiretroviral therapy is based on complex life-long therapeutic regimens that include a variety of drugs encompassing different times and modes of administration often burdened by a broad a spectrum of unexpected adverse events and drug toxicity.
A relationship between a suboptimal patient's adherence to antiretroviral treatment and virologic failure has been recognized since the early introduction of combination antiretroviral therapy (cART). Very high adherence rates are required to achieve a sustained virological response measured as HIV undetectable viral load (plasma HIV-RNA levels <20 copies/mL), containment of risk of development of drug resistance, favourable immune system recovery, and reduction of risk of transmission of HIV infection itself [1].
Poor adherence is related to some immutable factors such as age, sex, schooling and cultural background while others can be prevented by ensuring a favourable relationship between patient and health care personnel [5]. Current guidelines of antiretroviral therapy underline the importance to enforce an educational counselling pathway, that should be continually provided to the patient [6, 7]. Clinical pharmacist plays a key role working together with the physician in the HIV outpatient clinic, with particular benefit on giving information about drugs, ADRs monitoring, drug interactions and patients' adherence surveillance [8].
Aim of this study is to assess improvements on patients' adherence to cART and to monitor and promptly signal ADRs in an HIV outpatient clinic in a tertiary teaching hospital in Italy, after having established a pharmacist-physician based co-operation program [9, 10].

PATIENTS AND METHODS

Overall, 1056 patients were regularly followed-up in the HIV outpatient clinic of the S. Orsola-Malpighi teaching hospital where a dedicated hospital pharmacist has been introduced since February 2012 in the multidisciplinary clinic team.
Pharmacist's tasks included to provide correct information on risks and benefits of all drug therapies potentially involved in the care of

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Table 1 - Self-report of cART adherence, use of co-medications and nutritional supplements, and eventual adverse events, distributed and collected to every patient taking cART at our outpatient centre.

Date _____ Patient's ID _____

Which antiretroviral agents are you taking?
1._____ How many tablets/capsules per day? _____
2._____ How many tablets/capsules per day? _____
3._____ How many tablets/capsules per day? _____
4._____ How many tablets/capsules per day? _____
5._____ How many tablets/capsules per day? _____

Where do you usually take your medications:?
Only at home _____ At home and outside _____ Outside only _____

Did you take all medicines during the past week-end?
No_____ Yes_____

How many times did you miss a dose, during the past week?
Never_____ 1 dose_____ 2 doses _____ >2 doses_____

How many times did you miss a dose, during the past month?
Never_____ 2-3 doses_____ 4-6 doses _____ >6 doses_____

Does someone remind you to take your medicines?
No_____ Yes_____

Did you suffer from any disturbance?
No_____ Yes_____

If yes, which disturbances?
1._____
2. _____
3. _____
4. _____

Did you take other medicines, nutritional supplements, or other drugs, during the past month?
No_____ Yes_____

If yes, which medicines, nutritional supplements, or integrators?
1. _____
2. _____
3. _____
4. _____

Did you discontinue one or more prescribed medications, when you eventually experienced some disturbance?
No_____ Yes_____

Which antiretroviral medicine did you discontinue, in particular?
_____

Did not notice some change in your physical/morphologic change?
No_____ Yes_____

If yes, did these changes involved predominantly:
Face_____Abdomen_____Limbs_____Other_____

HIV infection and related disorders, monitoring adherence to the cART, evaluate the side effects reported by the patient and tracking therapeutic misprescriptions.
A ten-item questionnaire to be answered by the patient (Table 1) was provided in order to investigate patients' adherence, to assess any eventual use of concurrent drugs and/or nutritional supplements, and any concurrent unexpected events experienced since the last visit, according to the suggestions from previous studies [3, 10-14].
Concurrently with the distribution and the accountability of antiretroviral drugs, the hospital pharmacist delivered the cART questionnaire regarding adherence and adverse events to be returned at any subsequent monthly access by each patient during prescriptions refill. All information were recorded in a pre-designed database for data elaboration and analysis.
The reliability of information disclosed in the self-reported questionnaire were verified through a double-checking by the hospital pharmacist with patient interview at the time of drug distribution and figures recorded on a dedicated patient database regarding all drug refills and number of tablets dispensed.
Only questionnaires returned by our patient population between February and May 2012 were considered for this study, accounting for 659 patients. Patients were stratified according to the number of missed drug doses per month and levels of adherence were identified as follows:
- 0 (no) missed doses per month: 100% adherence;
- 1 missed dose per month: 95-100% adherence;
- 2-3 missed doses per month: 90- 95% adherence;
- 4-6 missed doses per month: 80-90% adherence;
- 7 or more missed doses per month: <80% adherence.

The impact of the above-defined adherence to cART was assessed in relation to absolute CD4+ T-lymphocyte counts, and plasma HIV-RNA levels, prospectively acquired in our patient cohort.
With regard to adverse events, physical (morphological) changes, early gastrointestinal and early neuropsychiatric disturbances have been analyzed, according to previous literature studies, and the updated antiretroviral management guidelines [2-4, 6, 7, 9].
Data obtained were stratified according to cART regimens prescribed and due to the previous way drugs were supplied, with medical personnel directly involved in the process, we were also able to measure time saved in physician working hours to be translated in extra time dedicated to patients during the visits.
Statistical examination has been performed using MedCalc (MedCalc Software, Acacialaan 22, B-8400 Ostend, Belgium) and Student t test, Mantel-Haenszel chi-square test were calculated where appropriate.

RESULTS

Adherence reports of 659 patients were analyzed. Males accounted for 74% of total sample size. Average age was 44.2±15.2 years, average length of HIV-disease was 9.6±4.3 years. Our population consisted in 64% past or current drug abusers, 24% homosexuals, 12% heterosexuals. Eleven percent of patients met AIDS definition criteria at least once. Average lymphocyte CD4+ count was 486±188/mm^3, patients with undetectable HIV viral load were 68% at time of initial data recording while average HIV viral load in those with detectable viremia was averagely 4.6 log10 copies/mL. Sixty-two percent of patients returned at least one questionnaire during the period evaluated. Demographic characteristics of age and sex in patients who returned the questionnaire were similar to those who did not, although we could observe an increased rate in psychiatric diseases and addiction problems in the latter group. This probably caused a slight overestimation of adherence in the represented cohort. Four hundred and eighty-five out of these 659 patients (74%) ensured a complete adherence rate (100%) to the prescribed cART, 102 (15%) were 95-100% adherent, 57 (9%) were 90-95% adherent, 12 (2%) showed a 80-90% adherence and only 3 had an adherence rate below 80%.
Patients who suspended their cART for short periods (more than consecutive 72 hours) due to any disturbance reported were only 1% of those reporting a 100% adherence rate while the percentage rose to 33% among patients with adherence levels below 80%, suggesting a reverse relationship between adherence levels and risk of cART suspension.
Concurrent use of other drugs (multiple pharmacotherapy) seemed to deteriorate cART adherence as while 53% of patients with a reported 90-95% adherence rate to cART were on

multiple medication regimen, the number increased to up to 58% and 67%, in those patients with cART adherence rates of 80-90% and < 80% respectively. Furthermore, to confirm that adherence rate gets worse with an increasing number of tablets/capsules taken daily, we observed that 100% adherent patients consisted of patients on one-to-three tablets/capsules per day regimen for a 61% of total, while the remaining 39% of subjects received four or more tablets/capsules per day. On the other hand, lowest adherent patients had a prescription of one-to-three tablets/capsules per day accounting for the 33% of total, while 67% were on four or more tablets/capsules per day regimen (Figure 1).

In order to highlight if adherence to cART influenced HIV progression in our patients, we analyzed variations of mean value of absolute CD4+ T-lymphocyte count and mean levels of plasma HIV-RNA of 57 selected patients with an elevated adherence rate (>95%) (Group 1), compared with those of 56 patients showing only a slightly lower adherence rate (90-95%)

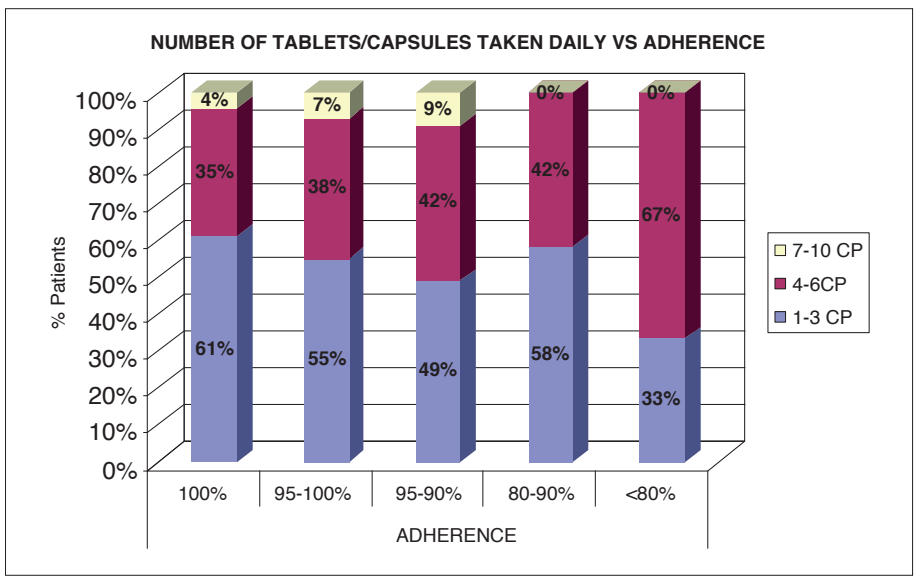

Figure 1 - Assessment of cART adherence, based on the number of antiretroviral tablets/capsules to be taken daily.

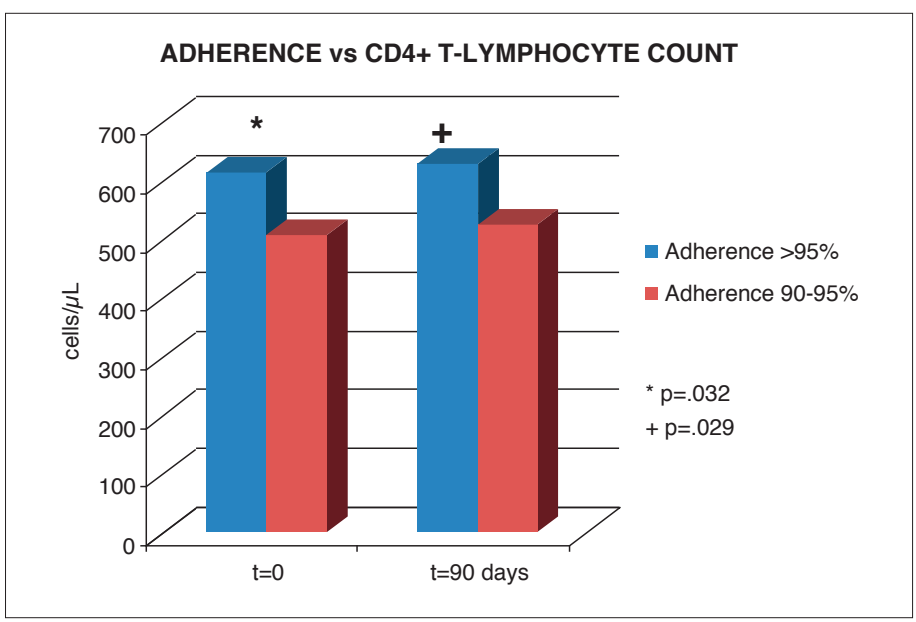

Figure 2 - Patients' adherence levels, compared with absolute CD4+ T-lymphocyte count.

(Group 2) from day 0 (when surveillance begun), to day 90. Patients were matched for sex, age, and average time on cART. CD4+ lymphocyte count proved to be greater in Group 1 versus Group 2 patients.
When considering the mean plasma HIV-RNA levels, although lower levels were always detected in Group 1 compared with Group 2, this difference did not reach a statistically significant figure in both the last available clinical control (51 versus 376 HIV-RNA copies/mL; p=.061), and in the previous one, conducted three months before (73 versus 393 HIV-RNA copies/mL; p=.058) (Figure 2). However, when we take into account the percentage of patients with a completely suppressed viremia (i.e., HIV-RNA levels below 20 copies/mL), this last, remarkable virological target has been attained with a significantly more elevated frequency in patients belonging to Group 1 as opposed to those of Group 2, both in the last available clinical control (82% versus 66% of patients; p<.001), and in the previous laboratory control, performed three months before (73% versus 58%; p<.001) (Figure 3).
We also found that when compared to previous years, when antiretroviral drugs were simply distributed by staff physicians, the presence of a dedicated hospital pharmacists enabled the physicians in charge to deliver an improved assistance to HIV-infected patients in terms of dedicated time for visits and increased number of both scheduled and urgent visits.

DISCUSSION

Our results demonstrate that an optimal adherence to cART (defined here as an assumption of over 95% of prescribed doses) was associated with increased mean absolute CD4+ lymphocyte count, and a better virological suppressive effect as shown by the increased number of patients with a persistent undetectable HIV viral load. Similarly to what other authors have found, sub-optimal adherence to cART and concomitantly poor adherence to attend clinical and laboratory follow-up checks are some of main determinants of a possible virological failure, although many other items, such as genetic, gender, and inter-individual pharmacokinetic/pharmacodynamic features must be taken into account [15, 16].
We believe that a better assistance for the management of cART is possible if every patient is seen by different health care professionals within a multidisciplinary approach to HIV disease and its management. That can lead to an increased patient-caregiver alliance, and an improved self-awareness of the patient itself to be devoted to his/her life-long cART regimen. A synergetic health care assistance provided by both hospital pharmacists and staff physicians is an extremely valuable instrument for a reliable assessment of all aspects aspiring to an optimal cART consumption. A correct management of all untoward events and an accurate evaluation of patient's adherence represent an

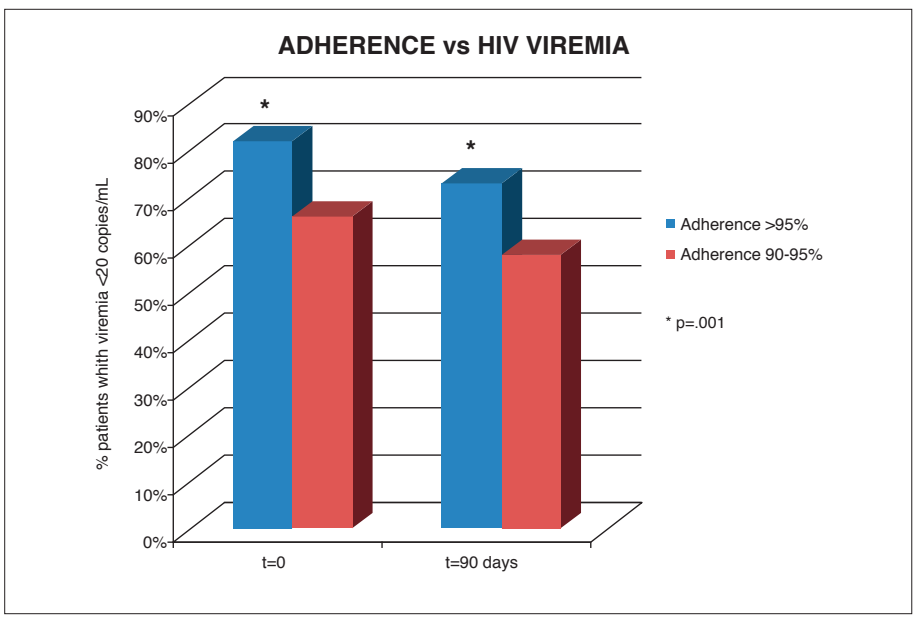

Figure 3 - Patient' adherence levels, compared with HIV viremia.

optimal strategy, to ensure and tailor the best therapy to each single patient and situation, and also to consider an optimized planning of the available resources [17-20].
The recognition of an insufficient adherence to cART and/or untoward events, and that of the possible causes leading to these alert conditions, enables to the pharmacist-physician team to intervene in a timely manner, and start all actions aimed at ameliorating patient's compliance and tolerability issue, i.e. resorting to a therapeutic switch, to simplification strategies, or to a pharmacological or a psychological support, when deemed necessary.
The pharmacist/physician team can promptly recognize presence of alert conditions for cART failure such as insufficient adherence or early development of ADRs through a reciprocal sustain and good coordination, allowing to intervene in a much shorter time by undertaking measures to improve patients' compliance to cART and resolve tolerability issues. Active monitoring of both adherence and toxicity issues becomes even more important in those subsets at increased risk of low adherence levels, hence with a bigger risk for virological failure, such as patients in their elderly, those affected by comorbidities, immigrants, substances and alcohol addicts and patients suffering from psychiatric or neuro-cognitive disorders. [2, 3, 6, 7, 13, 14, 18].
A correct management of all drugs concerning HIV disease by the concurrent intervention of dedicated hospital pharmacists together with physicians is expected to provide the best level of assistance, in terms of comprehensive health care delivery and also in planning the future resources of our HIV outpatient clinic.

Keywords: HIV infection, antiretroviral therapy, patient's adherence, adverse event, outpatient management.

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SUMMARY

Permanent monitoring of adherence to combination antiretroviral therapy (cART), together with the assessment and management of related adverse events, plays a key role for optimised management of HIV infection. In our HIV outpatient clinic a dedicated pharmacist provides direct drug distribution and accountability, and gives information on administration mode, possible side effects and drug interactions. A survey card regarding cART adherence and adverse drug reactions (ADRs) is administered to all patients. All figures are recorded in an electronic database. In an *ad interim* analysis 659 consecutive patients' data were evaluated, of whom 74% were fully adherent to cART. A lower adherence rate was found to be correlated with the presence of concurrent medications, and with the increasing number of daily cART tablets/capsules. A significant impact of cART adherence on a favourable course of the main laboratory surrogate markers of HIV disease progression (CD4+ T-lymphocyte count and HIV viral load) was also observed. Darunavir-containing cART was related to a lower incidence of early gastrointestinal and neuropsychiatric disturbances and also a reduced perception of morphological/physical changes. A multidisciplinary approach based on strict interaction between pharmacists and infectious diseases physicians may significantly improve cART adherence and the monitoring of adverse events, making a considerable contribution to the better management of HIV-infected patients.

RIASSUNTO

Un monitoraggio permanente dell'aderenza alla terapia antiretrovirale di combinazione (combination antiretroviral therapy, *cART), unitamente alla valutazione e alla gestione degli eventi avversi correlati, gioca un ruolo chiave nell'ottimizzazione della gestione dell'infezione da HIV. Nei nostri ambulatori dedicati all'infezione da HIV, un Farmacista Ospedaliero dedicato effettua la distribuzione e valuta eventuali effetti collaterali e l'aderenza alla cART, fornisce informazioni sulle modalità di assunzione, sugli eventi avversi e sulle possibili interazioni farmacologiche. A tutti i pazienti viene somministrata una scheda riguardante l'aderenza alla cART e l'eventuale percezione di effetti indesiderati. Tutti i dati vengono registrati in un database elettronico. In questa analisi* ad interim, *sono stati valutati i dati relativi a 659 pazienti consecutivi, il 74% dei quali presentava un'aderenza alla cART del 100%. Abbiamo rilevato una correlazione tra bassi livelli di aderenza e uso concomitante di altri farmaci, e con il numero di compresse/capsule di farmaci antiretrovirali da assumere quotidianamente. È stato inoltre evidenziato un impatto significativo dell'aderenza alla cART su un decorso favorevole dei principali marcatori surrogati di laboratorio di progressione della malattia da HIV (conta dei T-linfociti CD4+, e viremia di HIV non dosabile). Prendendo in considerazione la tollerabilità, i regimi cART contenenti darunavir apparivano correlati con una più ridotta incidenza di eventi avversi precoci, sia sul versante gastrointestinale che su quello neuropsichiatrico, e sulla percezione di modificazioni fisiche-morfologiche. Un approccio multidisciplinare basato su una stretta interazione tra farmacista e medico infettivologo può incidere in misura significativa sull'aderenza alla cART e sul monitoraggio degli eventi avversi, fornendo un notevole contributo a migliorare il livello complessivo di gestione ambulatoriale dei pazienti con infezione da HIV.*

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