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New horizons in the pharmaceutical care of HIV patients on long-term antiretroviral treatment

Nuevo horizonte en la atención farmacéutica del paciente VIH con el tratamiento antirretroviral de duración prolongada

Mercedes Gimeno-Gracia[1], Antonio Antela[2]

[1]Department of Pharmacy, Hospital Clínico Universitario Lozano Blesa. Zaragoza. Spain. Coordinator of SEFH's HIV Patient Pharmaceutical Care Group. Aragon Healthcare Research Institute (IIS). Spain. [2]Infectious Disease Unit, Hospital Clínico Universitario, Santiago de Compostela. Spain. Member of GeSIDA (Spanish AIDS Study Group). Spain.

Author of correspondence
Mercedes Gimeno Gracia
Avda. San Juan Bosco, 15
50009 Zaragoza. Spain.
Email:
mgimenogrsalud@gmail.com

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Antiretroviral treatment (ART) has experienced a startling progress in the last few years as a result of the combination of safe and highly effective drugs that allow people living with HIV (PLHIV) to reach survival rates similar to those of the general population, and convenient dosing schedules whereby a single tablet a day is able to control infection and prevent transmission.

Spanish PLHIV will soon benefit from the first-ever long-acting ARTs: cabotegravir (CAB) and rilpivirine (RPV), indicated for patients on stable ART, with a consistently suppressed viral load (VL) (< 50 copies/mL) and no previous resistance or virologic failure to non-nucleotide reverse transcriptase inhibitors (NNRTIs) or integrase inhibitors (IIs). According to the products' SmPC, oral CAB and RPV must be administered for 4 weeks before initiation of long-acting ART to evaluate the patients' tolerability to the medication. Subsequently, a loading dose of intramuscular CAB and RPV (two injections, one in each buttock) is administered, followed by a maintenance dose. As none of the thousands of patients evaluated in the development studies suffered any adverse events during the lead-in oral phase, the responsible pharmaceutical company submitted the data to the EMA requesting that treatment with long-acting ART drugs may be initiated without a lead-in phase.

The efficacy and safety of long-acting ART medication has been demonstrated by the ATLAS and FLAIR phase III clinical trials, where long-acting ART administration for 4 weeks was shown to be non-inferior to oral ART in pretreated virologically suppressed patients. Between the two studies, a total of 6/7 cases of virologic failure to long-acting ART and 3/7 patients on oral treatment displayed resistance to the medication. In both studies, the two arms exhibited similar tolerability rates, although patients on long-acting ART developed grade 1-2 injection site reactions, most of which resolved by the seventh day[1-3].

The 700-subject ATLAS-2M trial included a combination of patients coming from the ATLAS trial and a group of patients previously treated with oral medication. Subjects were randomized into two groups, one receiving long-acting ART every 4 weeks and the other every 8 weeks. (at a 50% higher dose). At week 48, administration every 8 weeks showed itself to be non-inferior to administration every 4 weeks[4].

These studies included patients with appropriate disease control, normal renal and liver function, limited comorbidities and no hepatitis B coinfection. To be included, women had to be nonpregnant. Seventeen percent of subjects were 50 years old or older; women accounted for 27.5% of the sample, patients with a BMI > 30 for 17% and those of black race for 18%[3].

Several studies have highlighted the high interest in long-acting ART among PLHIV. A single-center US study (n = 374) showed that 61% of PLHIV were either willing or very willing to undergo long-acting ART therapy, with 41% expressing a preference for tablets, 40% for injections and 18% for implants[5]. A total of 54.7% of respondents to the Positive Perspectives survey (n = 2,389), administered in 25 countries, expressed a preference for long-acting ART. The three most cited advantages of ART were the decrease in long-term adverse events, the elimination of the burden of daily administration and a lower incidence of adverse events. Participants in the phase III trials indicated that long-acting ART boosted confidentiality and privacy, reduced the stigma associated with the disease and gave them a greater sense of freedom. An analysis of the patient-reported outcomes from the FLAIR and ATLAS studies concluded that patients preferred long-acting ART to oral therapy[6].

It must be mentioned, however, that several challenges remain regarding the introduction of the new long-acting ART medications[7], such as their incorporation to healthcare routines, their custody and ensuring that they are administered at the right time. Although administration of the treatment may occur at a different department in every hospital, pharmacists will still be in charge of informing patients about the therapy, providing them with

the relevant management recommendations, and following up on the evolution of their drug therapy in order to ensure that the best health outcomes are obtained. Management of missed doses or temporary changes to oral therapy when patients cannot come to the hospital (because they are away or on holiday) will be essential. The above-mentioned phase III trials contemplated a ± 7 day-interval; for longer intervals bridging oral therapy must be foreseen in order to prevent the development of resistance to the medication. Appropriate patient selection is also important for this therapy as subjects must have demonstrated proper adherence to ART for a long period of time.

A joint multivariate analysis that looked into the virologic failures that occurred in the ATLAS, FLAIR and ATLAS-2M trials identified the following potential causes for such failures: the presence of mutations associated to resistance to RPV, BMI > 30, low RPV concentrations at 8 weeks, and VIH subtypes A1 and A6[8].

As usual, hospital pharmacists are key in following up patients who initiate long-acting ART, as providers of recommendations for the proper management and administration of the medication and as professionals in charge of following up the evolution patients' drug therapy. Pharmacists have played the latter role since the outbreak of the HIV pandemic, working hand-in-hand with their infectious disease colleagues and with patients in order to improve health outcomes.

For more than five years hospital pharmacists have been working on the so-called CMO (Capacity, Motivation, Opportunity) pharmaceutical care model for outpatients, which envisages both a multidimensional kind of pharmaceutical care where hospital pharmacists play the role of medication experts vis-à-vis patients and their treatment, and an individualized approach to pharmaceutical care.

Implementation of the CMO model has resulted in encouraging health outcomes including enhanced adherence to ART, an increase in the number of PLHIV with undetectable VL levels, and an increase in pharmacotherapeutic indicators related to hypertension, dyslipidemia and diabetes[9]. The recent PRICMO study has shown an improvement in primary and secondary adherence to ART and to concomitant medication[10], while another study exhibited a more effective control of antihypertensive medication and a higher adherence to antiretroviral and hypertensive medication[11].

The increased prevalence of older PLHIV, who typically use polypharmacy and display higher pharmacotherapeutic complexity levels (mainly because of concomitant medications, potentially inappropriate medications, and drug-drug interactions), has prompted a review of the medicines prescribed to these patients to optimize their medication regimens. Hospital pharmacists are directly involved in these initiatives[12-14]. High pharmacotherapeutic complexity is related with a lower quality of life in PLVIH[15].

Despite the unquestionable improvement that the advent of the new long-acting ART medications will represent for many patients, the need of an individualized, multidimensional and multidisciplinary follow-up will make it indispensable to monitor patients closely both through traditional follow-up visits and through the incorporation of new technologies.

In a nutshell, the continuous work of hospital pharmacists in the care of PLHIV will be increasingly important going forward given their ability to relate to patients and manage their drug therapy.

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