Review

Long-acting agents for HIV infection: biological aspects, role in treatment and prevention, and patient's perspective.

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SUMMARY

Current cART regimens are highly potent and well tolerated, but long-term toxicities, drug-drug interactions, lifetime costs and scarce option for multiclass failed patients could limit the efficacy of treatment itself. Long-acting formulations of antiretrovirals, which could potentially replace daily tablets, have been developed and are under investigation for prevention and treatment of HIV infection. Cabotegravir and rilpivirine represent the first drugs studied in this context. The aim of this review is to summarize the biological bases, the available information on completed and ongoing clinical trials and the potential development of long-acting regimens for the treatment and prevention of HIV infection.

Key words: HIV, antiretrovirals, long-acting compounds, prevention, patient's perspective
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INTRODUCTION

Despite the outstanding improvement in HIV outcomes in terms of both morbidity and mortality following widespread access to combined antiretroviral treatment (cART), some limitations in the use of oral therapies still persist. Firstly, current cART regimens are highly potent and well tolerated (Gill et al, 2010) resulting in excellent rates (higher than 90% in naive patients) of virological suppression, but suppression rates are strictly related to the level of daily adherence to therapy (Nachega et al, 2014). Secondly, long-term toxicities, drug-drug interactions, lifetime costs and scant options for multiclass failed patients could limit the efficacy of treatment itself. Since no eradication of HIV is currently possible, medications must be taken indefinitely in order to maintain virological suppression.

All these factors urge the need for different approaches to antiretroviral treatment in the near future. In this setting, long-acting (LA) formulations of antiretrovirals (ARVs) have been developed and are under investigation to potentially replace daily pills both for the prevention and treatment of HIV infection.

Pharmacologic and virologic plausibility

Several questions are related to the use of Long-Acting Injectable Antiretroviral Agents (LAIAA). As a list, we can include the optimal dosing interval (*i.e.* every 4 weeks or every 8 weeks – although at the present time a q4w strategy seems to be preferred), the need for an oral induction phase, as planned in the LATTE-2 trial, and the consequences in the eventuality of missed doses.

The need to develop a pharmaceutical approach with long-acting compounds stems from the fact that none of the currently available treatments for HIV is able to cure the infection, either as a functional cure or eradication (Lederman et al., 2016). With very few exceptions, all ARVs can cause drug resistance (Clutter et al., 2016) and this is closely related to compliance with treatments (Pham et al., 2009), which are life-long at this point in time. The long-acting formulations may facilitate the maintenance of virologic suppression due their long T ½, thus requiring a limited number of administrations over a given period of time (Landovitz et al., 2016).

The compounds developed so far are rilpivirine (TMC278) (Baert et al., 2009) and cabotegravir (GSK1265744) (Trezza et al, 2015). The evidence of their efficacy and safety has to be coupled with the demonstration of long-term virological suppression by a two-drug maintenance therapy (Spreen et al., 2013). Rilpivirine is currently registered for HIV-RNA values lower than 100,000 copies/mL, thus its use has to be considered with this limitation. cART containing both rilpivirine and cabotegravir allows for an induction phase that will ascertain patient tolerability, efficacy and

safety before embarking on the injectable maintenance therapy, as demonstrated in the LATTE-2 trial (Margolis et al., 2016). This maintenance phase with injectable drugs would also work also if patients on suppressive therapy come from other successful drug regimens. The very favorable pharmacological exposure will reach all available enzymatic targets, thus preventing the development of drug resistance while patients are on therapy. A different story may apply in the case of discontinuation of LA drugs or if a patient misses doses through erratic compliance. In particular, we have no data regarding virologic protection after the final injection of these compounds. If a patient withdraws from a trial, will the pharmacological "tail" still be protective or pose a serious threat for the development of drug resistance? We know that dolutegravir, and likely cabotegravir, have a strong genetic barrier, but the same cannot be true for the nonnucleoside reverse transcriptase inhibitor (NNRTI) class. A single case of emergent NNRTI-resistant virus has been reported in a subject from a rilpivirine LA 300mg phase I tissue pharmacokinetic study (Penrose et al., 2016). Such a result would compromise further therapeutic options and may suggest protecting these LA injectable drugs with two effective oral NRTIs (Landovitz et al., 2016).

A consequence of the administration of these LA compounds will be a more favorable adherence profile. As we all know there is a tight interplay between adherence and virological suppression, and drug resistance, as shown by Nachega et al. A lower pill burden was significantly associated with both better adherence and virological suppression in 19 studies including 6,312 adult patients (Nachega et al., 2014). Likely due to safer and more effective drugs and improved patient adherence, recent data dealing with the epidemiology of resistance to ARVs showed a declining prevalence of HIV-1 drug resistance in experienced individuals in Western Europe (SEHERE collaboration) with the exception of NNRTIs (De Luca et al., 2013).

The impact of missed doses and the consequent development of drug resistance must also be considered when prevention trials are designed (Arya et al., 2015.). LA pharmacokinetics may not be sufficient in non-adherent patients and the consequences of this insufficient drug exposure could appear later on during the patient's life, without being immediately adjustable (Hickey et al., 2015).

A very recent report at the HIV Research for Prevention conference in Chicago described the emergence of a novel mutation in macaques that resulted in high-level resistance following the administration of subtherapeutic doses of long-acting injected cabotegravir (Andrews et al., 2016). This five amino acid (5AA) duplication at integrase position 232 made simian immunodeficiency virus (SIV) resistant to all currently licensed integrase inhibitors. On the other hand, the clinical impact of this 5AA insertion is still unknown.

Clinical studies

The association between cabotegravir and rilpivirine has been studied in the LATTE trial, a phase 2b, multicenter dose finding study performed in Canada and USA, where ARV naive adult patients were randomly allocated in a 1:1:1:1 ratio to cabotegravir 10 mg once a day, 30 mg once a day, 60 mg once a day or oral efavirenz 600 mg once a day plus two NNRTIs for an induction phase of 24 weeks. Patients virologically suppressed at 24 weeks were then randomly assigned to a two-drug maintenance regimen consisting of the allocated cabotegravir dose plus oral rilpivirine 25 mg or continued efavirenz plus NRTI for an additional 72 weeks. The primary endpoint of the study was the achievement of < 50 c/ml of HIV-RNA according to the FDA snapshot algorithm at 48 weeks. After the induction phase, 86% in the cabotegravir groups vs 74% in the efavirenz group had < 50 c/ml, whereas at 96 weeks, after 48 weeks of maintenance treatment, 82% in the cabotegravir groups vs 71% in the efavirenz group had virological suppression. Moreover, less adverse events (51% vs 68%) were reported in cabotegravir vs EFV (Margolis et al., 2015).

This study provides two major results. Firstly, it provides a consistent profile of long-term viral response with treatment regimens containing the INI analogues of cabotegravir and dolutegravir compared to EFV, as previously shown by the SPRING-1 and SINGLE studies (Stellbrink et al., 2013; Walmsley et al., 2015). Secondly, this study indicates that the two-drug maintenance regimen (cabotegravir plus rilpivirine) provides viral suppression that is at least similar to that of a three-drug regimen containing EFV.

Considering that efficacy, safety, tolerability, viral resistance and pharmacokinetics parameters were similar among the three doses of cabotegravir in the study, by a priori criterion the dose of 30 mg was selected for further assessment. This study represented the background for development of long-acting injectable formulations and the subsequent design of studies of cabotegravir and rilpivirine.

Cabotegravir 30 mg once a day orally, cabotegravir long-acting formulation and rilpivirine long-acting formulation are under investigation in the LATTE-2 study (Margolis et al., 2016), a phase IIb, multicenter, randomized study in which, after an induction phase of four weeks with cabotegravir 30 mg os/die+ABC/3TC 1 cp/die, patients were randomized 2:1:1 to cabotegravir LA 40 mg IM+RPV LA 600 mg Q4W, cabotegravir LA 80 mg im+RPV LA 800 mg Q8W, cabotegravir 30 mg os/die+ABC/3TC 1 cp/die (Figure 1).

The study enrolled 309 patients (91% male, 20% non-white), 289 entered the maintenance period. 95% and 94% of patients in the cabotegravir LA+RPV LA groups Q8W and Q4W, respectively, maintained HIV-RNA<50 c/ml at week 32 compared with 91% on 3-drug oral ART. The tolerability of the injection phase at 32 weeks leading to discontinuation (2 out of 230 IM recipients, both in the Q8W arm) was good. Drug-related adverse events through weeks 32 included injection

site pain (92% of patients) with 99% of injection site reactions being mild (82%) or moderate (17%), decreasing in frequency after the first injection. In a patient-reported evaluation (19) even though patients suffered from site injection pain, the majority were satisfied and willing to continue the IM treatment. In particular, comparing patients with the oral arm, patients in the IM arms were more satisfied in particular in terms of flexibility, convenience and lifestyle.

PATIENT'S PERSPECTIVE

The patient's perspective represents a milestone in the history of long-acting ARV formulations. Data on patient acceptability are very scarse. Some years ago, a survey among 400 patients was performed on their willingness to be administered ARV therapy parenterally rather than orally (Williams et al., 2013). Overall 73% of patients reported their interests in trying injectable formulations of ARV therapy. Some arguments in support of this was the hope that the new formulation may lead to avoidance of forgotten doses, protection of patients' privacy and improvement in tolerability. On the other hand, some considerable risks have been hypothesized, such as pain, erythema, nodule formation at the injection site and the potential emergence of drug resistance because of the unpredictable drug concentration following a long-term interval between injections of the drug. Nevertheless, reports from patients are lacking and need to be produced in order to correctly hypothesize the role of long-acting agents in clinical practice.

For this reason, from April to June 2016, Nadir Onlus - a leading Italian Patient Advocacy Group (PAG) in the field of HIV/AIDS - conducted a web survey on People Living with HIV (PLWH) investigating preferences regarding LAIAA. A questionnaire was posted on the PAG's website (accessible at http://www.nadironlus.org; the site receives more than 20,000 hits per month). Although the population filling in a questionnaire via the Web is different in some characteristics from people filling in a face-to-face survey, we think that the use of the Internet for such a purpose is appropriate.

The respondents were asked the following: (1) demographic data and how HIV infection was acquired; (2) disease awareness aspects; (3) daily aspects of the assumption of traditional (i.e.: pills) HIV therapy; (4) knowledge of LAIAA and impact of traditional HIV therapy versus LAIAA; (5) preferences on the assumption of LAIAA and worries about adverse events.

Four hundred and eighty-eight (488) people completed the questionnaire. Of these, 472 (97%) were taking cART. Mean age was 45 years; 14% were women and 21% were HCV or HBV coinfected. 200 (43%) discovered HIV infection in the last five years, 96 (20%) between 6-10 years, 192 (39%) before 10 years. 68% were men who have sex with men; 352 (72%) respondents were well aware of the role of cART (i.e.: both as treatment and as TaSP - Treatment as Prevention), the need to carry

out periodic checks (470, 96%) regardless of adherence to HIV therapy, the importance of paying attention to polypharmacy and drug-to drug interactions particularly when also taking non-HIV drugs (89% also considering self-seeking information on the issue); 220 (45%) declare they were reassured by taking cART everyday, but 218 (44%) stated they sometimes feel tired of the situation: 172 (34%) took one pill a day, 134 (27%) two pills once a day, 164 (36%) more than 2 pills a day, 238 (49%) took daily non-HIV drugs for any reason. Concerning adherence, changing the routine worried only 166 (34%) respondents, even though 214 (44%) significantly change their daily habits more than once a month (in particular, 14% more than 6 times a month). Of note, 144 (29%) have problems in taking HIV therapy because of their relationship status and 76 (15%) because of their work setting.

Concerning LAIAA, 268 (55%) knew of their existence, 408 (83%) would very much appreciate the idea of not taking cART every day: 336 (69%) declared that the greatest benefit would be not having to remember to take the pills - so feeling "more free", 102 (21%) that travelling will no longer be a problem. Overall, 402 (83%) respondents would feel better with the idea of an injection every two months; 324 (66%) believe that "pills" are associated with "AIDS" in the collective imagination.

On preferences on the assumption of LAIAA, 298 (61%) would like to choose whether to do take the drugs at home or in hospital, 410 (84%) declare LAIAA convenient although taking daily non-HIV pills. In the scenario of injecting only in hospital, 148 (30%) respondents claimed a 'benefit' even if the injection should be done once a month, whereas 190 (39%) prefer every two months. Finally, 304 (62%) believe that efficacy and adherence are strongly related, since they would be disappointed in case of treatment failure while taking LAIAA and 368 (75%) respondents say that LAIAA are convenient even though they cause a little pain/swelling at the injection site.

From the survey, taking pills is a big concern of PLWH taking cART. In this scenario, simplification with LAIAA may represent a crucial strategy to achieve the best results in terms of adherence improvement and quality of life. Simpler regimens may increase satisfaction with therapy and flexibility (i.e.: injection at home versus in hospital) is hoped. Of note, no particular concerns regarding potential contra of LAIAA (lack of adherence, need to be hospitalized, side-effects) were reported by patients.

Other long-acting drugs in development

Other LA drugs under development include MK8591, a novel NRTI, which in a phase 1 study single arm on ten naive patients, presented at CROI 2016, provided a mean t1/2 of 108 hours with a mean viral load reduction of 1.78 log10 at 10 days postdose (Friedman et al., 2016). Other very

interesting compounds are broadly neutralizing antibodies (bNAbs), 3BNC117 which reduced viral load up to 2.5 log10 after a single infusion in 17 patients, with a t1/2 of nine days (Caskey et al., 2015), and VRC01 in which a single infusion reduced viral load of 1.8 log in eight treatment naive patients (Lynch et al., 2015).

Long-acting formulation of cabotegravir for HIV-1 prevention

Data from the clinical PrEP trials with daily TDF or Truvada demonstrated a reduction of the risk of HIV-1 infection by 44-75% (Grant et al., 2010), nevertheless they showed a marked difficulty of patients to adhere to the daily oral regimen as only approximately 50-80% had consistently detectable tenofovir, considered a marker of good adherence. Better adherence could improve the efficacy of PrEP, since the risk of HIV acquisition was found to be substantially lower among patients with detectable drugs compared to those with undetectable drugs (Grant et al., 2010). On the other hand, trials among young African women (VOICE, FEMPrEP) failed to show any efficacy of either daily TDF or Truvada mainly due to the scarce adherence of the particIpants (Van Damme et al., 2012; Marrazzo et al., 2015).

Long-acting ARV may reduce the component of poor adherence linked to daily dosing in this setting. Preclinical studies have demonstrated the potential role of LA cabotegravir in the prevention of HIV transmission and advancement of this compound into clinical trials. Two phase 2° studies, ECLAIR and HPTN 077, have been designed to assess the safety, tolerability and acceptability of LA cabotegravir in HIV-uninfected adults. The CLAIR study enrolled HIV-1 uninfected people from ten US sites (Markowitz et al., 2016), whereas HPTN 077 enrolled both men and women in Brazil, sub-Saharan Africa, and the US. Both studies were double blind placebo controlled and were similarly designed. They have a lead-in phase of 30 mg daily oral cabotegravir for four weeks followed by a one-week washout phase and intramuscular administration of 800 mg of LA cabotegravir every 12 weeks for three doses. The results of ECLAIR demonstrated that both oral and LA Cabotegravir were well tolerated, permitting continued development of Cabotegravir for PrEP; the absorption rate following LA Cabotegravir injection was faster than predicted by early PK population models, leading to higher peak and lower trough exposures; from 15% to 31% of trough concentrations were <PA-IC_{90}, whereas 30% to 37% were ≥4 × PA-IC_{90} across injection visits, below initial predictions, and given observed trough levels, an eight-week dosing interval is currently under evaluation; participant satisfaction with IM CAB LA injections was high, including a preference for injections Q12W compared with oral CAB once-daily tablets.

Regarding the use of long-acting rilpivirine for HIV prevention, this compound is now being evaluated in HPTN 076, a phase 2a trial on safety and acceptability enrolling 132 HIV-uninfected

low-risk women in the USA and sub-Saharan Africa in a 2 : 1 RPV : placebo randomization. The study consisted of a four-week oral lead-in followed by six injections of 1200 mg each every eight weeks, followed by a 32-week observational period during drug washout. Results are expected in early 2017.

As a general consideration, LA agents obviate the need for a daily or peri-coital pill-taking activity; nevertheless adherence to injections still requires an adherence with even infrequent injections. The clinical trials could not prove a stringent analysis of adherence due to the fact that injections are administered in a clinic-based setting, as a directly observed therapy strategy. If a LA agent becomes approved for prevention by regulatory agencies, issues regarding administration will require strict behavioural consideration. The injectable contraception literature suggests a high rate of nonadherence after initial injectable hormonal contraception use (Haddad et al., 2013) and for this reason, even a LA injectable PrEP formulation would not be expected to solve adherence challenges for all patients.

What the future holds

Many patients and physicians regard the advent of injectable ARVs as a true revolution in the clinical arena. There are still challenges that need to be properly assessed and thus the green light has still not been given for LA formulations. Nevertheless, there are more Pros than Cons at the present moment. The fact that the pharmacological profile allows for monthly or bi-monthly administrations is the main advantage and this could be the real game changer for PrEP strategies. The approach with LA formulations works perfectly for adherent patients but it is not yet elucidated if this would represent a real advantage, or a reward, for non-adherent patients. In this scenario, proper clinical trials have yet to be designed.

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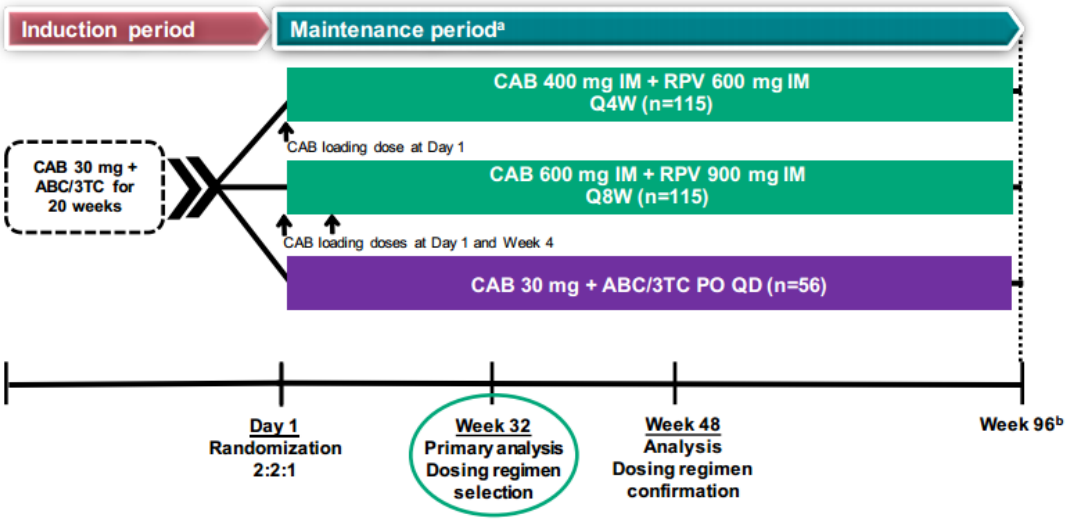
Figure 1. Design of the LATTE-2 study



ABC/3TC, abacavir/lamivudine; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter LA Extension Phase beyond Week 96.

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