

Less drug regimens and PI/r-based strategies in HIV infection: focus on best practices using the HIV patient's journey methodology

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SUMMARY

During these last two years less drug regimens (LDRs) in HIV, and in particular protease inhibitor (PI)/r-based strategies, have been explored both in clinical trials and in clinical practice. Many results are now available and more is known about how to use them safely and effectively. Understanding that an LDR strategy represents a real tailored therapeutic approach for the patient is crucial for the long-term success and positive management of HIV infection. Trust between patients and HIV specialists and a real focus on the patient's life are key factors for long life treatment success, in particular when using a LDR strategy. This is clearly shown by the HIV patient's journey (HPIJ) methodology, used in an Italian national workshop to better define the criteria and challenges of LDR strategies. This paper shows the results of this complex process.

KEY WORDS: Less drug regimens, Protease inhibitors, PI/r-based LDRs, HIV, HIV patient's journey.

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INTRODUCTION

Italian general setting

In Italy, the 'per year number' of persons with newly diagnosed HIV infection is permanently about 4,000 and this number does not seem to decrease over time (i.e. year/number: 2009/3,705; 2010/3,948; 2011/3,752; 2012/3,853). In 2012,

the 'surveyed' number of people living with HIV/AIDS (PLWHA) was 94,146, of these 11,674 (12,4%) and 82,472 (87,6%) were naïve and experienced with antiretroviral drugs respectively. The age of PLWHA was between 25 and 49 years in about 63% of cases and the expected duration of lifetime treatment was at least 40 years; of note, the 'estimated number' (i.e. including people unaware of their HIV status) of PLWHA ranged between 108,214 and 156,910. The recent attitude of starting earlier combined antiretroviral therapy (cART) aims at guaranteeing individual health (i.e. good long-term clinical conditions and high quality of life) and avoiding unaware virus transmission. Unfor-

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tunately, in Italy, 43% of newly diagnosed HIV infections are “late presenters”, meaning that diagnosis occurs in patients with T CD4+ <200 c/μL. Consequently, there is the urgent need to improve the management of the so-called ‘preceding steps’ (i.e. HIV-testing/response delivery/diagnosis/staging of disease) to favour patients’ prompt entry into a safe, efficient, and high quality *health journey*, that only HIV-specific clinical centres can ensure.

Nowadays, approximately 90% of cART-treated patients have undetectable viral load in plasma and their life expectancy is generally considered not very different from that of people without HIV, if their immune system is restored. Thus, HIV infection today is *de facto* a chronic non-progressive disease, with an increased incidence of co-morbidities related both to prolonged exposure to antiretroviral drugs and aging. Further in this scenario, increased health care costs - due to long-term management of the infection/disease - is a tangible topical issue, which cannot be postponed. In particular, the identification of safe, less expensive and validated lifetime therapeutic strategies are strongly advocated by physicians and patients, as well as health policy makers and planners.

In this regard, after starting a ‘*hard cART induction phase*’, that has the goal of achieving control of HIV RNA replication (i.e. <50 cp/mL) with the consequent reversal of T CD4+ decay, a ‘*softer cART maintenance phase*’ seems a reasonable option, mainly to lessen drug exposure, reducing long-term toxicity and managing the patient’s treatment fatigue (i.e. ‘*induction-maintenance strategy*’). Furthermore, ‘cART simplification’ in the maintenance phase (for instance by using a drug de-intensification strategy with some PI/r-based LDR options) could also enable the release of useful treatment resources essential for failing patients, who require newer and more expensive drugs.

The paradigmatic key to ‘successful cART’ (to be intended as elevated efficacy, good tolerability profile, best possible long-term quality of life) is the full understanding from the very beginning (i.e. HIV diagnosis) of all the patient’s needs, including the emotional attitude and approach to the disease and medications, both at individual and social level. An open-minded

collaborative relationship as well as an effective and empathic communication between the HIV specialist and the patient are the cornerstone for achieving the best possible results in all disease phases and should represent ‘the next generation’ methodological step.

Introductory considerations on LDR and PI/r-based LDR strategies

In recent years, LDR strategies, and in particular PI/r-based regimens, have been explored both in clinical trials and real world practice. Many results are now available and more is known about how to use them and for which patients they are suitable. Generally, in cART *naïve* patients LDR strategies can be considered only in particular situations (see below), because in this setting a fully active potent triple standard regimen has demonstrated better results in achieving virological and immunological treatment response compared to LDRs, in particular mono PI/r-based strategies. Consequently, there is no reason to deny a standardized treatment to patients at least for the first year of treatment (induction phase), starting triple therapy clinical trials being effective, solid and numerous, even if it is important to recall that also in this setting some clinical trials on LDR are promising (see below). Instead, the ‘real stage’ of LDR strategy is the ‘optimization’ setting (maintenance phase), longer than the induction phase, in which many new trials can now better allow the construction of a real tailored regimen for each patient, not only to tackle any current problematic clinical situation, but also to think proactively to avoid possible future complications.

The clinical-diagnostic management of LDR strategies and, in particular, PI/r-based LDR strategies should be based on a homogeneous and shared expertise and common national recommendations in all clinical centres, to avoid arbitrary prescribing decisions and to prevent budget-driven choices. Moreover, understanding by physicians and communicating to patients that a simplification with a LDR strategy is ‘one possible personalized strategy’ for a patient are essential. In particular, the following preliminary steps are crucial:

- The reasons for considering a LDR regimen should be explained to patients carefully and

extensively. As previously stated, these could be proactive or reactive and both physicians and patients should balance the potential advantages (e.g. the risk of comorbidities if proactive or management of comorbidities if reactive) and disadvantages (e.g. greater pill burden, more daily dosage, management of a hypothetical rescue strategy that could occur in 5% of subjects, in particular in case of non adherence or incorrect identification of candidates). Patient refusal of a LDR regimen should be considered a realistic possibility and obviously another option must be taken into account in this case.

- The correct identification of subjects is mandatory. The inclusion criteria for PI/r-based LDRs include medical anamnestic data, such as concomitant comorbidities (e.g. chronic hepatitis and others), concomitant drugs and demographic social data (e.g. occupational status/social life style, privacy concerns, pregnancy and desire of motherhood). To collect all these data, a particular emphasis should be placed on the fact that an appropriate, precise and comprehensible verbal communication should be used and a reciprocal trusting relationship (between the patient and the physician) should be put in place. If applicable, the 'patient's empowerment' could be an extremely useful approach for ensuring treatment success and his satisfaction. Besides treatment prescription, psychological screening and counselling on a correct lifestyle are indicated.

With regard to the patient selection for successful LDR strategies, the importance of immunological and virological markers (i.e. T CD4+ value and HIV RNA level) is today widely known (see below). In future, the identification and standardization of other laboratory markers (e.g. pro-viral DNA) for better identifying optimal patient-candidates could be of great advantage in clinical practice. During follow-up, specific attention to other details should be put in place to help the patient take all the advantages from the PI/r-based LDR regimen, in particular concerning the pre-emptive role of sub-clinical toxicity progression (bone mineral density, bone marrow, renal function, and cardiovascular disorders as well as metabolic abnormalities). Finally, the health care staff

of clinics and hospital pharmacies have to be clearly informed about the crucial role of medication adherence to avoid treatment failure, particularly in this context.

Patients and cART today

From the very beginning physicians should explain to patients that the current cART regimen could be periodically tailored to individual needs (and PI/r-based LDR strategies are one way to do this). Consequently, the regimen can be prescribed in a short, medium or long perspective. In future, cART may be further modified in symptomatic and asymptomatic patients or according to new acquisitions of scientific knowledge (e.g. not only the existence of triple standard therapy), but always remaining in a setting of safety and warranty. In any case, the aim of cART is to ensure the best possible life-long health condition and the possibility of changing therapy should be perceived as a potential benefit or as the most suitable therapy for *that* patient during *that* specific period.

Emotional factors and daily life issues are crucial for the better choice of every cART regimen: psychological evaluation should be performed, at the beginning and periodically, and the tight link between successful LDR treatments and correct adherence must be made clear at the outset. Patient empowerment should be ensured by informing and educating on basic scientific elements needed to understand the decision options for their 'long-life treatment journey': for this purpose patient's advocacy group educational materials should be considered.

MATERIALS AND METHODS

The HIV patient's journey

The HIV patient's journey (HPJ) is a SIMIT (Italian Society of Infectious and Tropical Diseases) initiative in collaboration with the ISTUD Foundation and the main Italian patient advocacy groups (ANLAIDS, NADIR, NPS Italia, PLUS), brought forward with the help of AIMI (Italian Nurses Association of Infectious Diseases) and SIFO (Italian Society of Hospital Pharmacy and Pharmaceutical Services of

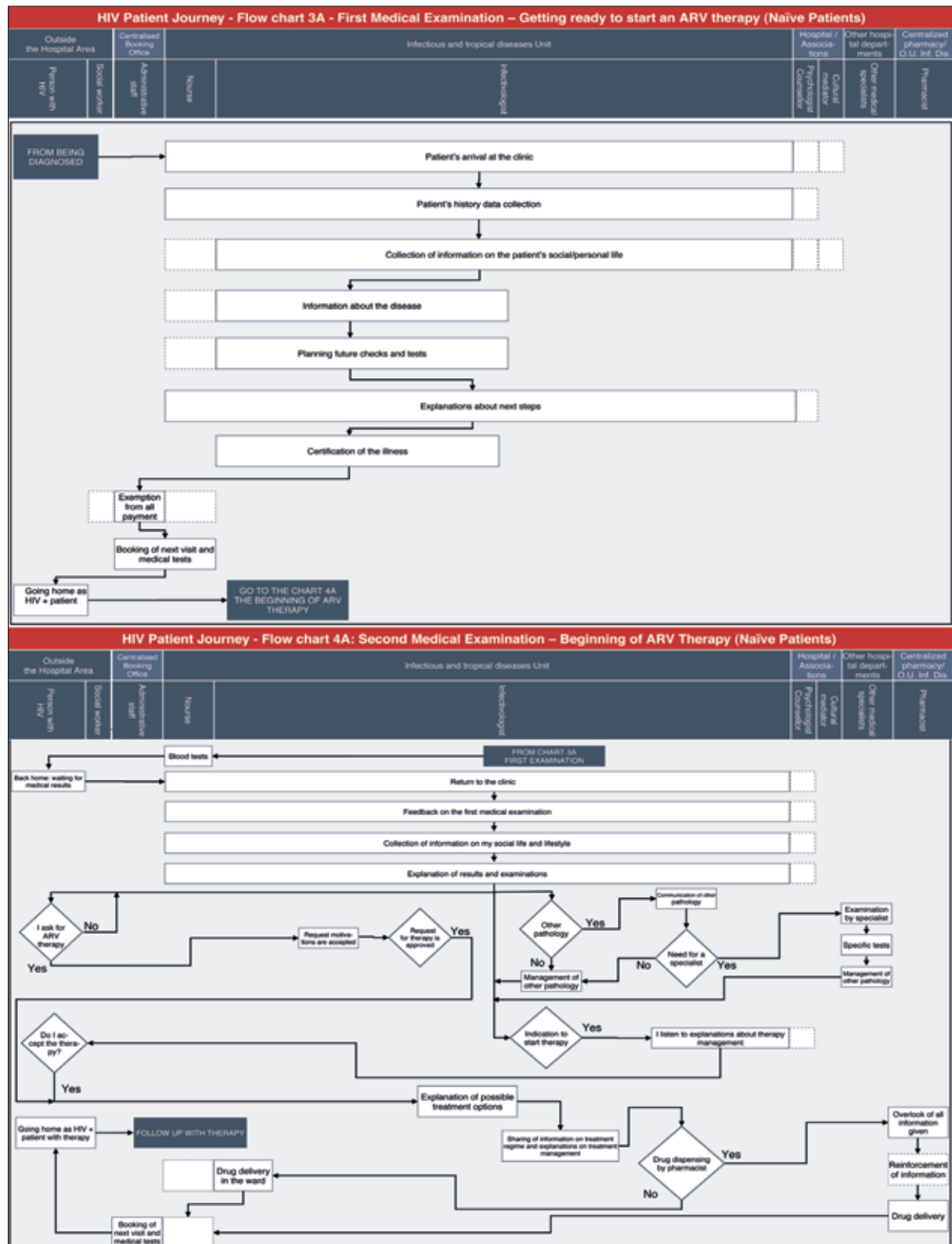


FIGURE 1

Healthcare Organizations), under the patronage of the ISS (Italian National Institute of Health) and the Ministry of Health.

The patient journey (PJ) is a patient-centred methodology aiming, from the patient's perspective, at mapping all the steps, relations, actors, emotions that the patient faces when approaching a health problem. The result of this process (specific for every disease) is a complex network of 'paths', both inside and outside the healthcare environment, that patient/person experiences from his/her diagnosis until the end of the care pathway (e.g. in HIV is 'death', being the disease a long life one). In particular, each journey of every patient is settled by the decisions taken on what are called 'decisional hubs' (DecHubs) of the PJ, that are situation/moments identified in the network where different actors (i.e. always the patient, often physicians, sometimes other actors) interact. Of note, the 'patient opinion' in a DecHub is strongly influenced by all different experiences (due to events, emotions, situations, people involved) the person goes through before facing a DecHub. Consequently, different experiences can change:

- 1) 'the patient opinion';
- 2) the final decision in a DecHub;
- 3) the following path in the PJ.

In this vision, DecHubs emerge as potential markers of quality management of the disease: physicians' capacity to understand all these factors, acting accordingly with a positive attitude as well as having effective and empathic communication is crucial. All the players mentioned above have put in place the PJ methodology for HIV (i.e. the HIV patient's journey).

Workshop methodology

A national workshop - promoted by SIMIT (Italian Society of Infectious and Tropical Diseases) with the patronage of the main Italian patient advocacy groups (ANLAIDS, NADIR, NPS Italia, PLUS), a local patient advocacy group (ASA), the associations/societies AIMI (Italian Nurses Association of Infectious Diseases), AMCLI (Italian Association of Clinical Microbiologists), SIFO (Italian Society of Hospital Pharmacy and Pharmaceutical Services of Healthcare Organizations), SIVIM (Italian Society of Medical Virology), the institutions

AGENAS (National Agency for Regional Health Services), ISS (Italian National Institute of Health) and the Ministry of Health - was set up to discuss in a multi-disciplinary setting the PI/r-based LDR strategies in current clinical practice. The faculty was composed of sixty experts divided into seven working groups: each group analysed a different topic concerning PI/r-based LDR strategies (except for group one). In particular:

1. Quality of care, patient insights and sustainability; key challenges and opportunities for capitalizing LDR strategies.
2. Quality of care, patient insights and sustainability; fitting patient's needs with LDR.
3. How to start the 'treatment journey' already thinking of LDR strategies: starting cART with a triple PI/r based regimen.
4. How to start the 'treatment journey' already thinking of LDR strategies: starting cART start with a 'potent dual' PI/r based regimen.
5. How to choose the right LDR option through the HIV patient's journey: optimization with a 'potent dual' PI/r based regimen.
6. How to choose the right LDR option through the HIV patient's journey: optimization with a 'easy (light) dual' PI/r based regimen.
7. How to choose the right LDR option through the HIV patient's journey: optimization with a mono PI/r based regimen.

One Rapporteur, one HPJ expert, one PI/r-LDR expert and one Italian HIV Guidelines connoisseur were identified for each working group and, together with the other members of the group, the HPJ methodology (see Figures 1, 2a-c) was followed to identify the most significant statements related to each topic. Each statement was ranked according to the scoring system used in the Italian National Guidelines:

- a) degree of recommendation: A, Highly recommended; B, Moderately recommended; C, Optional;
- b) level of evidence: I, data obtained from at least one controlled, randomized study with adequate power or from a meta-analysis of controlled studies; II, data obtained from non-randomized studies or from cohort observational studies; III, recommendation based on case reviews or expert opinion.

This paper summarises the results of this complex process.

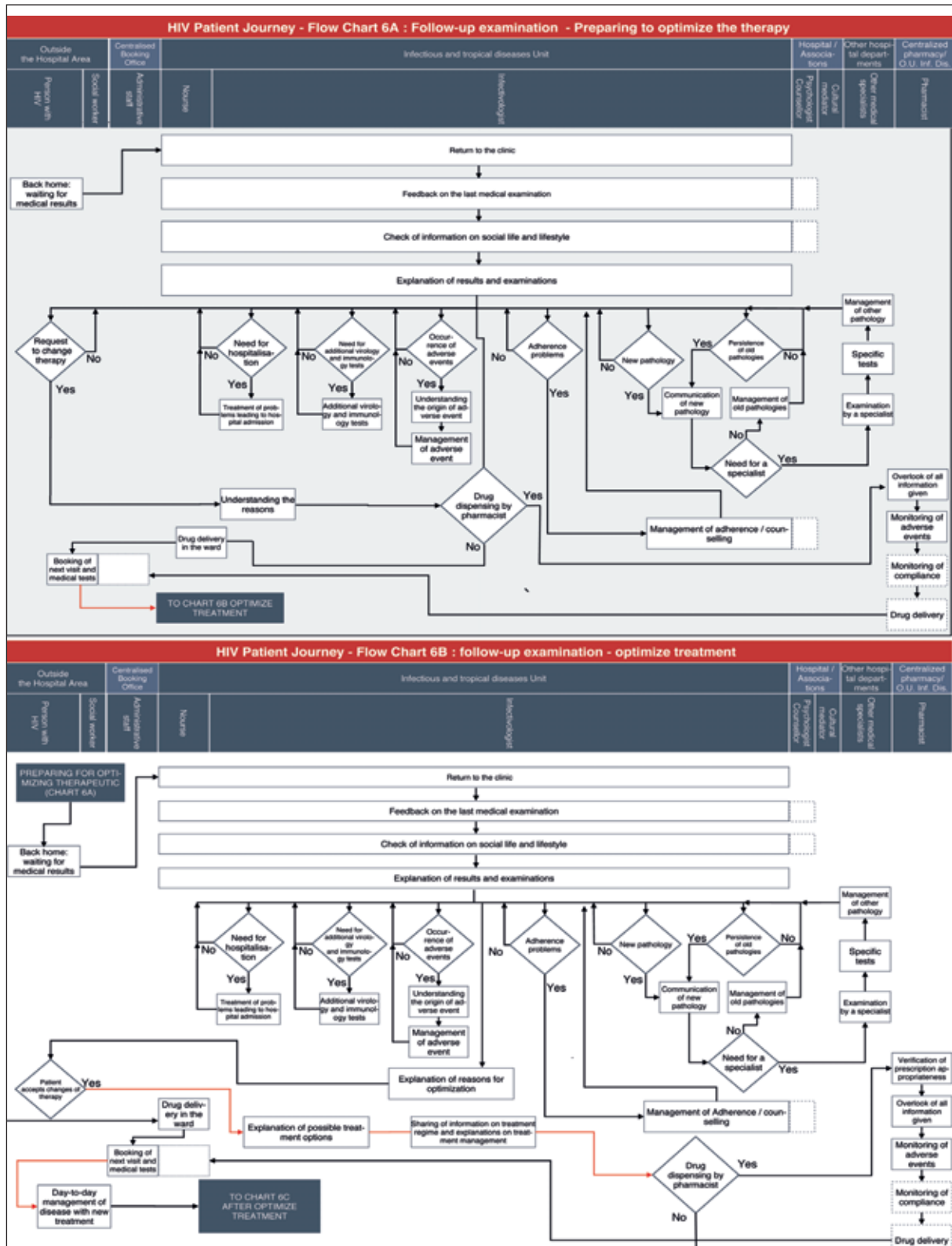


FIGURE 2a,b

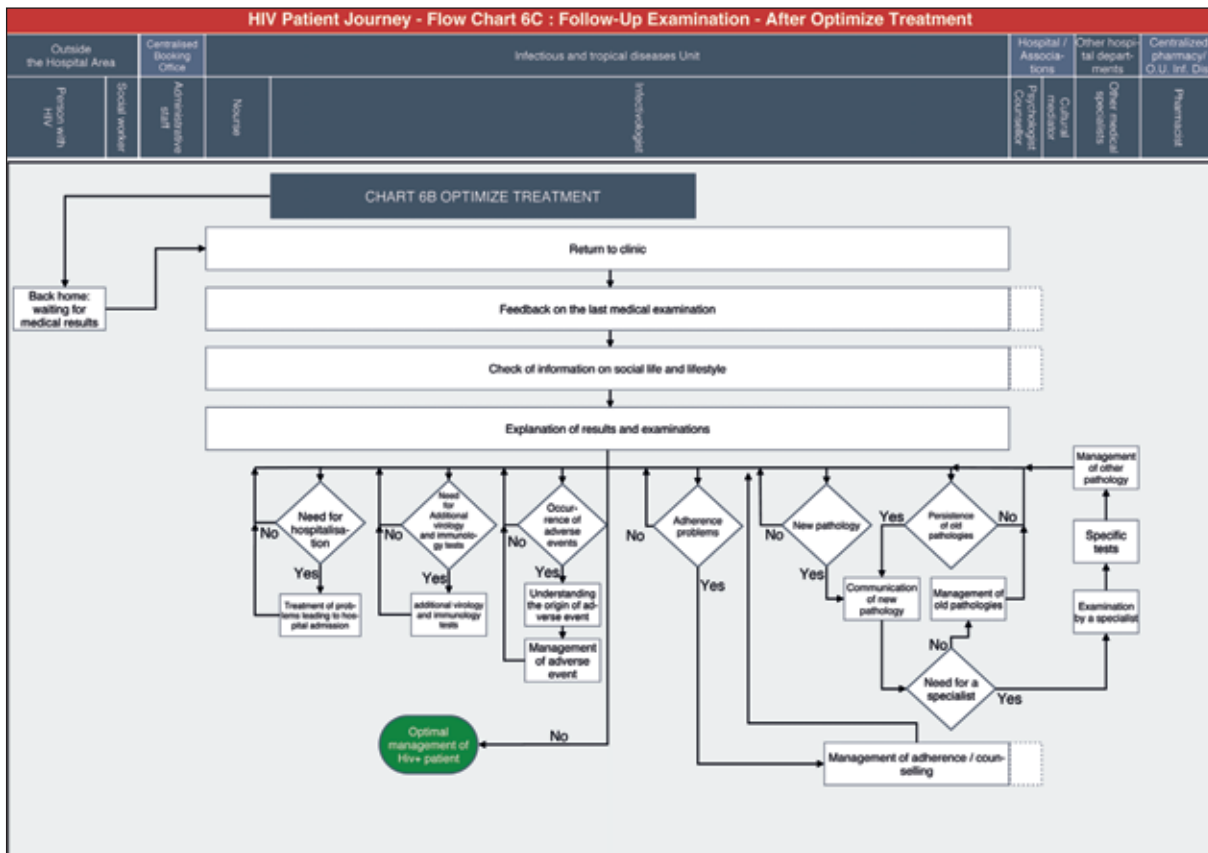


FIGURE 2c

RESULTS

General remarks on LDR strategies

According to current evidence, 'major tenets' for considering LDR strategies are:

- PI/r are key elements for LDR strategies due to their high genetic barrier [AI].
- Darunavir (DRV) + ritonavir as a booster (r) or Lopinavir/r (LPV/r - co-formulated) are PI/r best options according to available studies [AI].
- PI/r selection should be done according to their tolerability profile and the presence (or increased risk) of comorbidities [BIII].
- T CD4+ nadir needs to be >100/ μ L [AI].
- Drug pharmacological compatibility (when selecting a dual regimen) should be checked [BII].
- Absence of HBV and HCV co-infection is required [AI] (for exceptions see below).

Moreover, the following aspects are strongly instrumental to the success of LDR strategies:

- Achievement and maintenance of optimal adherence is mandatory [AI].
- Patients' empowerment is highly advocated (see above: 'Patients and cART today') [AIII]: in particular patients need to be informed about the reason for considering an LDR strategy, on its *pros* and *cons* versus a standard triple strategy [AIII]; they need to understand and share the choice [AIII]; they need to know that eventually additional monitoring during follow-up can be required [AIII].
- As shown using the HPJ methodology, an *entry visit* for evaluating the possibility of an LDR strategy, a *decisional visit* for prescription, and a *follow-up visit* for monitoring/evaluation should represent the best standard in good clinical practice' (see Fig. 2) for maximizing the expected benefit from the simplified therapeutic strategy and for ensuring an allied and motivated patient [AIII]. Monitoring of outcome measures defined at baseline and communication of the results

may be used to enhance the patient's motivation [AIII].

PI/r-based LDRs can be employed in the following type of patients:

- cART *naïve* (only dual LDRs): in the presence of a) drug resistance to NRTIs, but not PI/r at GRT or b) co-morbidities (caution for cardiovascular disease - CVD and/or risk for).
- cART experienced for treatment optimization if both of the following conditions are met:
 - Documented HIV RNA <50 cp/mL for at least 12 months while the patient is on continuous treatment [AI], and
 - T CD4+ cell count >200/μL at the time of simplification.

In general, LDR strategies should be avoided if:

- There is the persuasion (either by the physician or the patient) that triple antiretroviral therapy is the best possible choice in that specific case [AIII];
- There is not sufficient knowledge by the physician and/or enough empowerment by the patient concerning LDR strategies [BIII].

Obviously, refusal of the LDR strategy by the patient can occur and another treatment option must be offered [AIII].

Starting cART with a triple PI/r-based regimen in view of a PI/r-based LDR strategy

Triple PI/r-based regimens are among the first choices recommended in International and Italian Guidelines, and particularly used by clinicians when a prompt start of cART is needed but genotype resistance testing (GRT) is still ongoing. In this setting, it can be useful to consider and score all the comorbidities (cardiovascular/renal/bone/liver/metabolic) and/or their risk factors, according to the information available, that could influence the choice of the specific PI/r, bearing in mind that their management requires a multidisciplinary approach and particular attention to drug-drug interactions.

A PI/r-based triple starting regimen (mainly, but not exhaustively with DRV/r or LPV/r) in view of an LDR strategy can be considered in:

- Advanced naïve patients awaiting GRT;
- Patients with HIV RNA >100.000 cp/mL awaiting GRT;
- Patients with non-nucleoside reverse-transcriptase inhibitor mutations at GRT;

- Patients with non-amplifiable GRT;
- Major depression or other psychiatric disorders (warning on interactions);
- Patients with HIV-associated neurocognitive disorders (HAND);
- Patients with Kaposi's sarcoma;
- Pregnancy or motherhood desire;
- Patients at potential risk for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)-related toxicities.

Particular attention to the spine, considering Abacavir (ABC)/Lamivudine (3TC) as first choice, should be considered in:

- Patients with estimated glomerular filtration rate (eGFR) <70 mL/min/1.73 m²;
- Patients with renal insufficiency and/or osteoporosis;
- Post-menopausal women.

Information and empowerment of the patient, on the need for a long-life cART by implementing an individualized antiretroviral 'treatment journey' based on an induction-maintenance strategy (see above) should be initiated from the very beginning [AIII].

Clinical practice and PI/r-based LDR strategies for naïve patients

Dual PI/r-based regimens are indicated as starting regimens only in the presence of NRTI drug resistance and/or specific comorbidities (caution for CVD and/or risk for, see above) [BII] and consequently the strategy has to be considered an *alternative*.

Monotherapy, instead, is generally discouraged [AI]. Based on the evidence in this setting (the degree of recommendation refers to the patient subsets considered) LPV/r appears to be the best PI/r option for the purpose: LPV/r + Raltegravir (RAL) (PROGRESS Study) [AI], LPV/r + 3TC [AI, GARDEL Study], LPV/r + Maraviroc (MVC) 150 mg [BI, VEMAN Study] are the regimens to be considered. DRV/r 800/100 mg + RAL (NEAT 001 Study) is also recommended. Other regimens, such as Atazanavir (ATV)/r + MVC 150 mg, DRV/r 800/100 mg + MVC 150 mg (MODERN Study), ATV + RAL (SPARTAN Study) cannot be recommended [AI] because they showed less virological efficacy than standard triple regimens.

Selection of the antiretroviral combination should consider pharmacological interactions

between drugs; published data on LPV/r and RAL, 3TC and MVC are encouraging.

First laboratory assessment, evaluation of tolerability, monitoring of comorbidities and neurocognitive performance should be performed according to standard clinical practice [BIII] and have to be shared with the patient [BIII]. Adherence should be closely monitored according to the usual assessment procedures [AIII]. Recommended interval between follow-up visits should not exceed three months [AIII].

Reasons for considering a reactive switch to PI/r-based LDR

Reaction to a specific clinical condition or a patient's wish is surely 'the main driver' for a physician to start thinking of a new therapeutic strategy. Here we summarise the main aspects that can lead to a PI/r-based LDR choice.

Presence of comorbidities

- **Renal:** patients with mild kidney disease (CKD 2) and/or related genetic factors related and/or at high risk of CKD (diabetes, arterial hypertension) [BII]; overt kidney disease (CKD stage 3-5) [AII].
- **Bone:** patients with osteopenia and increased turnover of related markers [BII]; with osteoporosis and/or osteoporotic fractures [AII].
- **Lipoatrophy:** for partial reversion or prevention of its worsening [AIII], for management of metabolic abnormalities [BIII].
- **General:** for all other kind of NRTI-associated comorbidities [AII].

Presence of toxicities

- In patients with NRTI-associated toxicities [AI].

Presence of resistance

- In patients with resistance to NRTIs [AI].

As previously stated, a PI/r-based LDR strategy for reactive reasons is usually proposed by the physician, but could also be requested by the patients, if informed on its existence. In both cases it is important to point out that the meaning and implications of the LDR choice need to be extensively explained in the clinical encounter [AIII].

Reasons for considering a proactive switch to PI/r-based LDR

A proactive attitude (i.e. some minor labora-

tory abnormalities, patient's wish or treatment fatigue) is a trickier driver for considering a new therapeutic strategy. In fact, this approach implies a flexible reasoning, a long-term vision and a conscious and cautious attitude both by physician and by the patient. Here we summarise the main aspects that can lead to a PI/r-based LDR choice.

Risk of comorbidities

- **Renal:** patients with increased risk of kidney disease + presence of Tenofovir Disoproxil Fumarate (TDF) exposure especially when associated with PI/r [AII].
- **Bone:** patients with un-modifiable risk factors for osteopenia (e.g. genetics, menopause) [BII]; with increased risk of osteoporosis or osteoporotic fractures + presence of TDF exposure especially when associated with PI/r [AII] and after intervention on all modifiable factors [AI].
- **Laboratory abnormalities:** for managing some minor laboratory metabolic abnormalities [BIII].
- **General:** prevention of comorbidities that are potentially worsened by NRTIs [BIII].

Risk of toxicities

- Prevention of NRTI toxicity [AII].
 - Prevention of mitochondrial toxicity [AII].
- In particular, PI/r monotherapy switch strategy could be considered a *strategic option* irrespectively of the current risk of NRTI-related toxicity, in order to preserve antiretroviral treatment options, reduce the risk of NRTI-related toxicity and save health care costs. However, data from randomized strategic clinical trials are not yet available [CI].

A PI/r-based LDR strategy for proactive reasons can be proposed by the physician or can be requested by the patient, if informed about its existence. It is important to point out that in both cases, the meaning and the implications of the LDR choice need to be explained extensively during the clinic visit [AIII].

Caution for PI/r-based LDR strategies

Here we have summarised some warning conditions for using a PI/r-based LDR strategy.

- Presence of cardiovascular disease (CVD) [AIII] and/or high risk for CVD [BIII].
- Presence of neurological symptoms or previous HIV-related symptomatic neurocogni-

tive impairment [AII]. In this situation avoid monotherapy [AI].

- Presence of the M184V mutation and/or historical genotypes in the retro-transcriptase. In particular, if monotherapy is not indicated for any reason, avoid dual PI/r + Emtricitabine (FTC) or 3TC regimens [AI].
- Presence of major mutations of resistance to PI/r. In this situation, avoid the PI/r-based LDR strategy [AI].
- Under the cut off limit of R5-tropic virus and/or in historical genotypes. In particular, if monotherapy is not indicated for any reason, avoid the PI/r + MVC strategy [AI].

Moreover, in the setting of viral hepatitis co-infection, PI/r-based LDRs can be used only in HIV/HCV co-infected patients with comorbidities or using Interferon (IFN) + Ribavirin (RBV) treatment [BIII] and in HCV/HIV co-infected patients eligible for anti-HCV treatment with or without direct acting agents (DAAs) [BIII]. According to the present evidence, LPV/r is the preferable choice. Instead, PI/r-based LDR strategies generally cannot be used in HBV co-infected patients, with the exception of patients who are candidates for Entecavir or PI/r + TDF [AI].

Clinical practice and PI/r-based LDR strategies for undetectable patients: decisions and monitoring

In this context, as previously outlined, PI/r-based LDR are indicated both for reactive and proactive reasons. In particular:

- If HIV RNA <50 cp/mL for at least 12 months and the patient is 'on continuous treatment' [AI].
- If T CD4+ cell count >200 c/μL at the time of switch.

Depending on the published studies, the following regimens should be considered:

- Dual Drugs strategies: PI/r + FTC/3TC [BII]; PI/r + MVC [BIII]; PI/r + RAL [CI], a PI/r + NNRTI [CI]. RAL and MVC regimens are considered 'potent', meaning they induce immunological reconstitution more quickly. Studies in the references show particular dosages of some drugs used.
- One drug (monotherapy) strategy: DRV/r [AI] or LPV/r [AI].

First assessment after switch (HIV RNA and T CD4+ count) should be performed after 1

month [BIII]. Monitoring of comorbidities and/or toxicities and neurocognitive performance should be done regularly according to standard clinical practice and should be shared with patients [BIII]. Adherence should be closely monitored according to the usual procedures of assessment [AIII] and the recommended interval between follow-up visits should not exceed 3 months [AIII].

Pharmacoeconomic aspects

By reducing the number of prescribed drugs, LDR strategies often lead to a reduction of medication costs, as already demonstrated in some countries, such as the UK, Spain and Italy, for the use of PI/r monotherapy. Moreover, LDR can also decrease the occurrence of cART-related toxicities and complications: for instance, the frequency of chronic renal failure, which is a growing and extremely expensive condition in HIV-infected patients. This in turn can further impact overall health care costs, releasing economic resources that may be used for HIV prevention and earlier treatment initiation. Interesting data from Emanuela Foglia are available in this issue of *Newmicrobiologia*.

CONCLUSIONS

Are LDR strategies a new tool to better 'serve' the HIV population?

Some general principles in the management of HIV-positive patients are well captured in the HPJ and should be applied independently from the chosen therapeutic regimen. For instance:

- A good patient-physician relationship and shared decisions are associated with greater patient satisfaction.
- All everyday life aspects, as well as emotions and perception of the disease should be evaluated and considered in the decision-making therapeutic process.
- High medication adherence is a well-established factor of treatment success, independently of the regimen prescribed.
- A reactive attitude to comorbidities or preventing them by estimating their risk, according to guidelines, should be performed in each patient on a regular basis.
- Prescription of antiretroviral drugs in the

presence of specific resistance associated-mutations is generally not recommended. Today, studies confirm that some PI/r-based LDR strategies have a good efficacy performance and can be safely used, as indicated in the Italian National Guidelines (where pros and cons for choosing an LDR strategy or not are well explained) and stated in the specific document by the Italian Medicine Agency (AIFA) (i.e. monotherapy). In the setting of cART optimization, LDRs are considered strategic and personalized choices among available cART simplification strategies. In fact, even if not suitable for all types of patients, LDR strategies may instead potentially be very useful in the management of some of them, 'tailoring' the regimen according to the patient's needs. All these considerations make us more confident than two years ago in using LDR strategies when applicable and optimistically we expect that future trial results and real world experiences will hopefully clarify the knowledge gaps still open at present.

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The following references are displayed by logical topic and in alphabetical order for each topic. The reason is

that they have all been used to compose the above texts with due care and weight.

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