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The Less Drugs Regimens (LDRs) therapy approach in HIV-1: an Italian expert panel perspective for the long-term management of HIV-1 infection

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The complete members list of the Multidisciplinary Italian Expert Panel on LDR is in the acknowledgment session.

INTRODUCTION

The standard treatment approach in HIV-1 infection involves a combination of at least three antiretroviral (ARV) drugs, i.e. highly active antiretroviral therapy (HAART), to fully suppress the plasma HIV-1 RNA viral load (VL). Currently, recommended first-line antiretroviral regimens consist of two nucleoside (NRTI)/nucleotide (NtRTI) analogue reverse transcriptase inhibitors combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r), or an integrase strand transfer inhibitor (INSTI). Furthermore, standard subsequent-line regimens involve an HAART approach, with at least a triple combination of ARV drugs.
For the first time, the Italian Guidelines on the use of ARV (I-ARVGL) published in the previous issue of New Microbiologica introduced the concept of LDR (Less Drugs Regimen), i.e. an ARV treatment regimen involving fewer than 3 standard agents combined. This concept refers primarily to an induction/maintenance therapy strategy, namely a standard three-drug regimen used to achieve virological suppression followed by an LDR regimen to maintain viral control, allowing at the same time the management of comorbidities, limiting or avoiding long-term toxicity, preserving future drug options, sometimes reducing the daily pill burden improving adherence and, consequently, improving the patient's quality of life.
The choice of suitable patients and the timing of LDR initiation are critical to avoid virological failure and the emergence of resistant viruses. The general considerations for a successful antiretroviral therapy with triple combination strategies also apply for LDR:

– High viral load (>500,000 copies HIV-RNA/ml) correlates with an increased risk of treatment failure;

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– The combination regimen used should preferably have a high genetic barrier;
– Archived resistance mutations in the mononuclear cells of peripheral blood are associated with ARV treatment failure;
– The presence of virus with CXCR4 receptor tropism is associated with a faster decline in CD4+ T cells and disease progression;
– Compartmentalised virus with drug resistance mutations in the central nervous system can cause the failure either of first-line therapy or the simplification strategies;
– High levels of viral DNA in circulating lymphocytes or residual viraemia are both associated with virological rebound and failure of simplification strategies.

Consequently, a detailed analysis of different settings (naïve, stably-suppressed patients, viraemic early-experienced patients, triple-class failure patients) and the possibility of using an LDR strategy are described. The implications on pharmacological compatibility, co-morbidities, neurocognitive aspects and patient-physician communication are also explored.

The LDR strategy is the first 'drug schematic simplification' step in a very long-term therapy approach that is currently available for HIV-1 patients in order to achieve wellbeing and disease control. Changing treatment in this perspective could be a feasible new option that needs to be understood both by patients and physicians in order to manage this life-threatening disease.

A multidisciplinary Italian Expert Panel on LDR, composed of physicians, patients, payers, economists and institution members has reviewed all HIV literature related to LDR and, on the basis of own specific expertise, has developed statements to define the right setting to use LDR strategies, highlight potential benefits and define the limits. To achieve this goal they followed a process which included meetings, teleconferences and a final workshop where all the Panel members shared, discussed and voted all statements developed.

METHODOLOGY

The main aim of the final workshop was to discuss in a multidisciplinary setting the topic of Less Drug Regimens in the context of HIV treatment. The Steering Committee of the event was composed of 10 Core Experts (CEs), who identified 6 thematic areas to be discussed:

– Virology;
– Therapeutic strategies;
– Drug toxicities;
– CNS protection and psychiatric distress;
– The role of communication in the patient and doctor relationship in the context of LDR;
– Pharmacoeconomic and regulatory aspects.

Afterwards 6 Core Expert Clinician Groups (CECGs) were organized, according to the 6 areas identified, composed of CEs (one or two per area) and Expert Clinicians. The CECGs had the task of identifying the scientific literature and writing a draft of statements to be discussed during the final workshop. Each CECG identified a Research Fellow, having the role of scientific secretariat for the coordination of the preliminary work, and a Rapporteur, who was in charge of presenting and explaining the statements during the final workshop.

Statements were ranked according to (I-ARVGL).

Degree of recommendation (only positive statements scored):

a) Highly recommended;
b) Moderately recommended;
c) Optional.

Level of evidence:

1. Data obtained from at least one controlled, randomized study with sufficient power or from a meta-analysis of controlled studies;
2. Data obtained from non-randomized studies or from cohort observational studies;
3. Recommendation based on case reviews or expert opinion.

At the final workshop 108 experts, mainly HIV specialists, were invited. It was organised as follows: during the morning there were several main lectures focusing on general issues related to HIV infection and treatment, and the statements were read by Rapporteurs. In the afternoon 6 Expert Groups (EGs, one per area) were composed, in which CECGs members and other HIV specialists analyzed the critical points, the pros and cons of the strategy from every specific aspect and preliminary discussed and possibly modified the CECG drafted statements.

The following day, all 108 experts voted all the statements of every area shown by Rapporteurs. They were approved when at least 75% of participants agreed with them; if agreements account-

ed for less than 75%, statements went back to EGs and were modified according to suggestions of the panel to be voted again. They were definitely withdrawn in case of maintenance less than 75% agreement.

Naïve patients: studies, virological aspects and strategic implications

The tailoring of the antiretroviral regimen is recommended to improve treatment outcomes in HIV-infected patients. Several factors should be considered when selecting a starting regimen. In particular, the emergence of resistance mutations and toxicities associated with NRTI and/or NNRTI represent a critical point in the selection of an optimal antiretroviral regimen. The development in clinical practice of dual therapies, based on the use of PI/r + RAL or MVC may represent an alternative to traditional regimens for long-term management of HIV-infected individuals. Consequently, a dual therapy including ritonavir-boosted protease inhibitors (PI/r) may be a potential and promising option also in antiretroviral treatment-naïve patients.

Several studies have investigated the efficacy in naïve patients of dual therapies based on PI/r associated with 3TC (LOREDA with LPV/r), with TDF (KALEAD with LPV/r), with efavirenz (ACTG 5142 with LPV/r), raltegravir (SPARTAN with ATV/r, PROGRESS and CCTG 589 with LPV/r, ACTG 5262 with DRV/r, RADAR with DRV/r) or with maraviroc (VEMAN with LPV/r; A4001078 with ATV/r).

To date, the most important and convincing results have been obtained with LPV/r at week 96 (PROGRESS Study). Indeed, LPV/r plus RAL showed non-inferiority versus the triple drug regimen LPV/r + TDF/FTC and also a statistically significant safer profile with regard to bone and renal damage, lipoatrophy recover, despite the fact that the lipid profile between the 2 arms after 96 weeks was similar.

A PI/r + MVC combination administered once a day at low dosage (150 mg) in patients with R5 tropism was also investigated. The most interesting data have been obtained with LPV/r at week 96, in the VEMAN Study, whose preliminary viro-immunological results are extremely encouraging.

In the ACTG 5142 Study, the LPV/r + EFV combination was very potent, but unfortunately revealed two major limitations of certain NRTI-sparing strategies: toxicity and the development of resistance.

Atazanavir does not seem to be the best companion either for maraviroc or raltegravir. Indeed, although the agent was unboosted and administered as 300 mg twice daily, results obtained in 2 randomised trials, the A4001078 and SPARTAN studies, showed that NRTI-sparing arms were inferior to standard care, in the former case as regards potency and in the latter as regards toxicity.

As far as darunavir is concerned, a preliminary single arm study, ACTG A5262, raised some concerns regarding the potency of the darunavir/r (800/100 mg) + raltegravir combination, especially in patients with a baseline HIV-RNA greater than 100,000 copies/mL. Moreover, darunavir CSF concentrations in patients taking the once-daily or the twice-daily dosage of the drug are different: recent data show that darunavir and ritonavir dosing not only significantly affects CSF concentrations, but also the extent of drug penetration into CSF in the once-daily dosage.

Monotherapy with PI/r is not currently recommended in naïve patients, as supported by the MONARK and ACTG A5262 studies.

Statements

The general rationales for the use of a PI/r as the backbone component of a dual regimen in antiretroviral-treatment-naïve patients are: high genetic barrier, sequenceability, pharmacokinetics, immunological T CD4+ recovery and tolerability.

- Considering its uniquely high genetic barrier, a PI/r should always be included in an initial dual regimen (AI).
- Dual therapies, based on the use of PI/r + RAL or MVC, represent a potential option for treatment of naïve patients at risk of NRTI toxicity and in the presence of NRTI resistance mutations (BII). In particular, dual therapy with lopinavir/r + RAL (AI) or MVC (BI) may be considered.
- Monotherapy should be discouraged.

Stably-suppressed patients: studies, virological aspects and strategic implications

The positive dramatic impact of highly active antiretroviral therapy (HAART) can be compensated by the entity of side-effects either at mid- and long-term and "therapeutic tiredness". These side-

effects are mainly due to NRTI and NNRTI exposure and could have an impact on long-term adherence. A complex interaction between the various elements, linked to both virus and host, could potentially lead to virological failure and drug resistance. The main aims of LDR include maintaining virological suppression and the long-term efficacy of HAART.

Potency and high genetic barrier are the main factors supporting the use PIs/r within LDR simplification regimens (both mono- and dual-therapy). The true backbone role of PIs/r is reflected in their capacity to drastically reduce HIV-RNA and not exclusively in their intrinsic antiviral activity. Their role in LDR simplification regimens cannot be matched by other compounds belonging to other classes in clinical use, such as integrase or CCR5 inhibitors. With this in mind, the activity of various inhibitors can be described by the equation: LPV/r = DRV/r > ATV/r.

None of the data available, often of poor quality and/or not recent, analyze cellular DNA or residual viraemia trends. Their role of these parameters in allowing the identification of patients eligible for switching, and the evaluation of the potency of all these treatment combinations have to be extrapolated from other therapeutic settings, such as treatment-naïve (MONARK study) or monotherapy-experienced patients. CD4+ nadir, plasma viraemia zenith and therapy duration with suppressed viraemia are common predictors of success, but need further validation.

Monotherapy

Extensive experience with LPV/r, particularly in the OK04 Study, and with DRV/r in the MONET and MONOI studies (different dosages analyzed) were seen to maintain HIV-RNA <50 cp/mL in subjects with suppressed viraemia at the start of monotherapy and absence of protease resistance associated mutations (RAMs) in previous genotypes. This makes LPV/r and DRV/r the drugs of choice for monotherapy in HIV-1 management, on account of their very high genetic barrier.

Virological control in subjects treated for a certain number of years should be the *sine qua non* condition for simplifying an antiretroviral regimen. This consideration is the main obstacle to a broader use of PI/r monotherapy by clinicians.

Good candidates for starting PI/r monotherapy are subjects with an undetectable HIV-RNA <50 cp/mL ("the lower the better") at the beginning of the strategy, who are fully adherent as seen during previous triple-drug regimens and who have been successfully treated for at least the last 12 months.

The extent of the HIV blood reservoir, measured as HIV-DNA, constitutes the potential viral span that could expand upon insufficient drug pressure. A lower cell-associated HIV load can favourably maintain viral suppression once PI/r monotherapy is started.

Dual therapy

PIs + RAL

Few studies have been published on suppressed patients switched to dual therapy containing PIs and RAL. A non-random-retrospective trial is available on 20 highly treatment-experienced patients who switched to ATV + RAL and were followed for 18 months. Five (25%) patients were switched before 12 months but maintained viral suppression.

In a 48-week single-centre, open-label pilot study in which 60 HIV-infected adults with plasma HIV-1 RNA (<50 copies/mL) on stable HAART (sHAART) were randomised (2:1) to lopinavir/ritonavir (LPV/r) 400/100 mg BID + raltegravir (RAL) 400 mg BID switch (LPV/r + RAL arm) or to continue on sHAART. The primary endpoint was the proportion of subjects with HIVRNA<50 copies/mL at week 48. Secondary efficacy, immunological and safety endpoints were also evaluated.

Demographics and baseline lipid profile were similar across the arms. Mean entry CD4 T-cell count was 493 cells/mm^3. At week 48, 92% (95% confidence interval (CI): 83%-100%) of the LPV-r/RAL arm and 88% (95% CI:75%-100%) of the sHAART-arm had HIV-RNA<50 copies/mL (p=0.70). Lipid profile (Mean ± SEM, mg/dL, LPV/r + RAL *vs*. sHAART) at week 24 was: total-cholesterol 194±5 *vs*. 176±9 (p=0.07), triglycerides 234±30 *vs*. 133±27 (p=0.003), and LDL-cholesterol 121±6 *vs*. 110±8 (p=0.27). There were no serious adverse events (AEs) in either arm. Regimen switch occurred in 3 LPV/r + RAL subjects (n=1, due to LPV/r + RAL related-AEs) *vs*. 0 in the sHAART arm. There were no differences between arms in bone mineral density, total body fat composition, creatinine clearance, or CD4+ T-cell counts at week 48. In virologically suppressed pa-

tients on HAART, switching to the NRTI-sparing LPV/r + RAL combination produced a similar sustained virological suppression and immunological profile as sHAART (KITE Study).

PIs + MVC

As far as MVC use is concerned, despite the relative abundance of data on naïve patients, little published data are available for suppressed subjects. The need for tropism testing before use of MVC in patients with suppressed viral replication may be overcome by the analysis of stored plasma HIV-1 RNA collected prior to suppression, or the use of proviral DNA obtained from PBMCs. Recent studies demonstrated a good correlation between tropism predictions from proviral DNA and results derived from viral RNA, however data from large cohorts and the overall clinical utility of this assay have yet to be determined.

Vitiello *et al.* published a small dataset on 20 suppressed subjects who switched to MVC-containing regimens and were studied for six months. Seven subjects were switched to MVC + DRV/r and one to DRV, and only one patient showed a rebound 4 months after switching from TDF, LPV/r and saquinavir to MVC+DRV/r therapy. The observation that the other subjects maintained a VL below 50 copies/mL after switching provides initial support for using proviral DNA to assess viral tropism.

The MVC dosage when used with a boosted PI, as derived primarily from the MOTIVATE trial, is 150mg BID. Nevertheless, pilot studies on naïve patients on dual therapy with a single MVC dose (300 mg or 150 mg) combined with LPV/r and ATV/r are available.

Due to boosting that completely abolishes liver excretion, meaning that the drug is completely excreted through the kidneys, MVC can be administered in dual therapy with a boosted PI at 300 mg od or at 150 mg qd if creatinine clearance is <80 ccs/min.

PIs + NNRTIs

The ATV + NVP combination has been tested in local experiences, but showed an unsatisfactory pharmacokinetic profile.

Switching to a nucleoside-sparing regimen of nevirapine + lopinavir/r in 34 subjects (compared to 33 with PI/r plus two NRTI) maintained full antiviral efficacy over 12 months, and suggests a reversion of nucleoside-associated mitochondrial toxicity. This association may be an option for avoiding mitochondrial toxicity (MULTINEKA Study).

One randomised, open-label study was performed on 236 patients who had virological suppression for ≥18 months and were switched to LPV/r BID + EFV or EFV + 2 NRTIs. After 2.1 years of follow-up, fewer drug-related toxicity discontinuations were reported and a trend toward a higher virological failure (VF) rate was seen with LPV/r + EFV in intention-to-treat and as-treated analyses.

Due to its high genetic barrier, etravirine (ETV) could be the best NNRTI to be used in combination with a PI/r in suppressed patients, however data on this combination in dual therapy are lacking. Adding ETV to a salvage regimen containing darunavir/r (DRV/r) significantly increased the probability of virological success, reducing and limiting the onset of PI-related resistance mutations in the DUET trials. Following these considerations and given the need to reduce long-term toxicity in treated patients, studies on dual combinations including ETV plus a potent PI/r (LPV/r, DRV/r and ATV/r) are urgently needed, taking into consideration PK interactions according to ETV available data.

PIs + NRTI (or NtRTI)

The only data available for this strategy concern switching to lamivudine (3TC) plus atazanavir/r (ATV/r). The ATLAS study demonstrated a sustained suppression of HIV viral load at 24 weeks after switching to 3TC plus ATV/r, with steady lipid tests and renal function improvement.

The efficacy of dual therapy including 1 NRTI and 1 PI/r was also tested in antiretroviral-naïve patients. The LOREDA pilot study demonstrated the efficacy of LPV/r + 3TC in suppressing HIV viral load in naïve patients, achieving >80% suppression in "as treated" analysis.

The KALEAD trial demonstrated similar efficacy when comparing co-formulated TDF/FTC plus LPV/r vs TDF alone plus LPV/r in naïve patients. Higher CD4+ increase and fewer metabolic disorders were also observed in the TDF-only arm.

Statements

– Monotherapy with a PI/r is indicated for HIV+ subjects who are virologically suppressed and

clinically stable under antiretroviral treatment (BI). This evidence comes from studies with LPV/r (BI) and DRV/r (BI), but not for ATV/r.
– Dual Therapy - NRTI sparing strategies - should always include a PI/r plus an NNRTI (BIII), raltegravir (AIII), or maraviroc (AIII).
– Dual therapy including 3TC/FTC and 1 PI/r can be used as an alternative to PI/r monotherapy when the latter strategy is not indicated (*i.e.* low CD4+ nadir, CNS involvement, etc.) (BII).
– In patients with Hepatitis B co-infection, the use of tenofovir (TDF) as single NRTI in combination with a PI/r is mandatory (AII).
– In stable patients with NRTI-associated toxicities, PI/r-based LDR can be considered both as monotherapy (BI) and dual therapies (BI-II).
– PI/r are the key drugs for avoiding the emergence of cross-resistance due to their high genetic barrier (AI).
– Based on available data, monotherapy with PI/r should be reserved (AII) for patients with:
  • No history of virological failure or major mutations of resistance to PI/r.
  • Suppression to <50 copies/mL for more than twelve months under continuous treatment.
  • CD4+ count greater than 200 cell/mm^3 at the time of the switch to simplification.
  • Nadir >100 cell/mm^3.
  • Optimal adherence.
– LDR can be also considered as a treatment option for pre-emptive switch in an induction-maintenance strategy in patients who started or included a PI/r (BII) in the presence of a stable immunovirological profile.

Viraemic, early-experienced patients (from 1st - 2nd lines): studies, virological aspects and strategic implications

Current guidelines state that the goal of therapy is to achieve and maintain HIV-1 RNA below detectable levels, with recommendations to change regimens upon virological failure because of the adverse consequences of higher levels of viraemia and viral evolution. Italian guidelines strongly recommend changing the regimen with at least 2, or, even better, 3 drugs, that are fully active in failing patients with viraemia >1000 copies/mL and genotypic resistance (AII); moderately recommend a regimen modification in patients with viraemia >1000 copies/mL without genotypic resistance mutations and in patients with persistent viraemic blips (BII), and do not recommend regimen modification in patients with isolated viraemic blips.

One major concern regarding the use of PI/r monotherapy is the potential for loss of control of compartmentalised virus in the cerebrospinal fluid or other sanctuary sites. For this reason, dual therapy companion drugs should have a high central nervous system penetration-effectiveness score.

One randomized multicenter study (HIV-STAR Study) using mono-LPV/r vs. TDF/3TC/LPV/r as second-line therapy in HIV-infected adults failing NNRTI-based HAART showed that at 48 weeks the proportion of patients with HIV-RNA <400 copies/ml in the mono-LPV/r-arm was 75% *vs.* 86% in the TDF/3TC/LPV/r-arm (p=0.053). The authors concluded that LPV/r monotherapy should not be recommended as a second-line regimen, or should be used with caution particularly in those settings where close VL monitoring is not available.

In the LDR setting, dual therapy including PIs/r could also be a suitable option in patients experiencing a first (or second) virological failure in the absence of any previous PI failure. In the event of documented NRTI toxicity, the rationale for the use of a PI/r as the backbone component of dual regimen is the high genetic barrier, toxicity, CD4+ recovery and few or no PI mutations detected at failure. However, these benefits may be overwhelmed by virological breakthroughand the development of resistance mutations to the companion drugs (efavirenz or raltegravir), thereby reducing the ability to keepdrugs or drug classes for future use.

Statement

For patients who failed their first (or second) regimen of 2 NRTI + 1 NNRTI, or 3 NRTI with no previous treatment failure to PI, dual therapies (based on the use of PI/r +RAL or +MVC for patients infected with R5 HIV-1) represent a potential treatment option (BIII).

Triple Class Failure (TCF) patients: studies, virological aspects and strategic implications

Building an effective salvage therapy must primarily be based on potency and genetic barrier,

and consequently a boosted PI is normally part of any dual drug salvage regimen. Sensitivity to the class accompanying the boosted PI should be warranted by lack of previous use and by co-receptor tropism analysis as recommended by current guidelines. If a CCR5 antagonist is considered, a low nadir CD4+ count should be viewed as a proxy for past X4 virus even if current R5 tropism is demonstrated. On the other hand, sensitivity to the boosted PI should be supported by cumulative analysis of all available HIV genotypes and a particularly careful review of patient treatment history. Indeed, the extent of previous exposure to PIs has been shown to be an independent predictor of triple salvage treatment failure in observational studies, including large datasets of cases used to validate genotypic resistance interpretation.

There is some indirect evidence that dual therapy based on a boosted PI plus an integrase inhibitor can be an effective rescue strategy in patients harbouring virus expected to be completely resistant to NRTI and NNRTI. However, residual activity of NRTI genotypically deemed ineffective has also been inferred in this context. By contrast, the contribution of inactive NRTI appears to be negligible when added to a three-drug salvage strategy or removed from triple therapy in the context of prolonged suppression of virus replication.

One plausible scenario where dual therapy based on a boosted PI plus an INI or a coreceptor antagonist (CA) is expected to be effective is previous failure to NRTI plus NNRTI therapy. When building a dual therapy regimen in this case, the same guiding principles derived from studies evaluating boosted PI plus INI/CA therapy in drug-naïve patients should be applied (e.g. possibly differential activity of different PIs combined with INI/CA).

Dual therapy can be considered in individual cases, particularly when toxicity issues and multiple previous failures discourage the use of several antiretroviral drug classes.

TCF is frequently associated with severe immunodeficiency and an immediate risk of disease progression, therefore the main goal in this setting is to achieve rapid control of viral replication and robust CD4 recovery. Preliminary data suggest the possibility of prescribing, even for TCF patients, effective and well-tolerated NRTIs and/or PI/r sparing regimens. Nevertheless PI/r are currently the salvage regimens of choice for the vast majority of patients.

Dual drug salvage therapy should only be used in cases where a boosted protease inhibitor (PI) is expected to maintain complete or substantial activity. Use of a high genetic barrier regimen based on a boosted PI is indeed recommended since the dual drug salvage regimen will most probably include a new but less robust drug class such as an integrase inhibitor (INI), a coreceptor antagonist (CA) or a fusion inhibitor (FI).

Statements

- Monotherapy is not a feasible option and dual therapy is not generally recommended as salvage or deep salvage treatment.
- A dual PI/r-based regimen may be considered as a simplification strategy in TCF patients who have reached undetectability with the crucial goals of reducing toxicities and saving options for the future (CII). In this case, the maintenance of fully susceptible agents in the regimen and a strict virological follow-up of the patient are mandatory (AII).
- In the presence of three active drugs belonging to other classes, use of NRTIs in salvage regimens is unnecessary, due to the extensive degree of resistance to this class (BII).

Pharmacological compatibility

The compatibility of the drugs combined in a regimen is a key factor for therapeutic success, and this is particularly true for LDRs. One aspect of drug compatibility is pharmacokinetic symmetry, meaning a substantial equivalence of the half-lives of the drugs in the regimen. In the SPARTAN study, where raltegravir was administered in combination with unboosted atazanavir (at the unusual dosage of 300 mg BID), an increased risk of selection of raltegravir resistance mutations was observed in patients with virological failure. This was thought to be related to the combination of the short half-life of unboosted atazanavir and the prolonged half-life of raltegravir (atazanavir is known to increase raltegravir concentration by 40-70%), leading to residual raltegravir monotherapy in the case of missed doses, and consequent increased risk of selection of resistance mutations.

It must be recognized that as long as adherence

is optimal there are no reasons for predicting treatment failure, regardless of pharmacokinetic compatibility (symmetry), while the problem emerges whenever drugs are no longer properly taken, and the residual persistence of drug concentrations following interruption is unbalanced, with a substantial risk of prolonged monotherapy with decreasing concentrations over time. The prototype of such a situation is represented by the NRTIs-sparing arm of the ACTG 5142 trial.

A second aspect of pharmacological compatibility is the lack of clinically significant drug-drug interactions. A couple of studies suggested that raltegravir decreases darunavir concentrations, however other pharmacokinetics studies showed the magnitude of this interaction to be negligible. The results of the ACTG 5262 trial, in which excess virological failure was observed in patients starting darunavir/r plus raltegravir treatment with a high baseline viral load, suggested that this interaction may play a role. However, pharmacokinetic analyses did not support any relationship between the risk of failure and darunavir concentrations. The reason for this unexpected failure rate could be related to the combination of poor patient compliance and limited forgiveness of the regimen containing raltegravir plus a boosted PI (not necessarily only with darunavir). However, data from large clinical studies (NEAT 001) are expected in the near future.

A second example is the compatibility between etravirine and PIs: interaction studies and clinical practice suggest a possible association with darunavir and lopinavir, but not with atazanavir, due to the significant decrease in the plasma exposure of the latter, however clinical data are still lacking. Furthermore, due to the significant difference in the elimination half-life between etravirine and PIs/r, etravirine monotherapy seems likely to occur in case of treatment interruption. Although etravirine has a stronger genetic barrier than first-generation NNRTIs, it does not mean that it can be taken into consideration in a setting of monotherapy.

A third aspect of pharmacological compatibility concerns the adequate dosing of drugs. It was recently suggested that maraviroc should be dosed at 150 mg qd when combined with a boosted PI, accordingly to a reanalysis of the MOTIVATE trial. In the pharmacokinetics sub-studies of two randomised pilot trials, maraviroc at 150 mg qd showed adequate plasma exposure when associated with lopinavir/r and atazanavir/r. However, broader clinical evaluation is required.

Darunavir CSF concentrations in patients taking the 800/100 once-daily or the 600/100 twice-daily dosage of the drug are different: recent data show that darunavir and ritonavir dosing not only significantly affects CSF concentrations, but also the extent of drug penetration into CSF in the once-daily dosage. This different CSF concentration also correlates with a statistically higher number of CSF escapes with 800/100 QD dosage vs 600/100 BID dosage. Interestingly, patients receiving darunavir/r QD showed not only lower CSF darunavir trough concentrations but also lower CPRs. An explanation for this could be the dose-dependant ritonavir inhibition of transporters present at the BBB. These findings might also be of interest in the light of the increasing attention being paid to DRV/r monotherapy, and especially to the doubts still concerning its activity into the CNS.

In conclusion, the status of current knowledge on the pharmacological compatibility of PI-containing dual regimens are in favour of LPV/r (with RAL 400 mg BID, MVC 150 mg QD, ETV 200 mg BID, 3TC 300 mg QD). Positive data are also available for DRV/r and ETV 200 mg BID, 3TC 300 mg QD (not with RAL 400 mg BID). Positive data are available for ATV and MVC 150 mg QD and 3TC 300 mg QD. Data on possible PI-sparing dual regimens (e.g, raltegravir and nevirapine) are still missing.

Statements

- PI/r monotherapies guarantee pharmacological exposure of the protease inhibitor comparable to that obtained in triple regimens (AII).
- When a dual therapy is chosen, the drugs' pharmacological compatibility should be considered (BII).

Co-morbidities

Cardiovascular aspects

Given the known association between NRTI (timidine analogues and d-drugs) and metabolic alterations (metabolic abnormalities and hepatic steatosis) it has been hypothesised that an alternative nucleoside analogue or a NRTI-sparing regimen could reduce CV risk. The other nucleo-

side backbones, based on ABC or TDF, cannot always be used as an alternative due their toxicity profiles. Concern has also been expressed regarding the potential CV risk associated with NRTI, and particularly with abacavir, however the potential mechanisms of this signal are not conclusive to providing a final answer.
Contrary to expectations, a significant worsening in lipid metabolism was seen in patients switching from TDF/FTC to the IP/r monotherapy arm (MONOI, MONET, MONARK). There were no statistically significant differences in the mean change from baseline to week 96 in lipid parameters in patients in LPV/r+RAL (PROGRESS study) or MRV (VEMAN study) vs. triple regimens LPV/r +FTC+TDF.
A recent analysis of Abbott clinical trials based on 3454 patients and pharmacovigilance do not suggest that rates of MI and CAD during LPV/r use are significantly elevated relative to the rate observed in the general American population. No study was able to show a significant change in FMD compared to baseline.

Liver
Several drugs should be used with caution in patients with underlying liver diseases. Thymidine analogue and zidovudine appear to have the highest risk of drug-induced liver damage, particularly in patients with viral hepatitis and /or NASH. Given the known association between NRTI (timidine analogues and d-drugs) and hepatic steatosis, it has been hypothesised that an alternative nucleoside analogue or a NRTI-sparing regimen could reduce hepatic toxicity. PI/r monotherapy + LPV/r + anti-HCV drugs have been shown to be as safe and efficacious as HAART + anti-HCV drugs (KAMON 2 Study).
Raltegravir has been shown to have a good liver safety profile in HIV/HCV patients. HCV co-infection is associated with an increased risk of HIV-related kidney disease, including proteinuria and acute renal failure, than HIV monoinfection.

Kidney
One recent publication evaluated the relationship between cumulative and overexposure to tenofovir and kidney outcomes in 10,841 HIV-infected patients from the Veterans Health Administration, who initiated antiretroviral therapy between 1997 and 2007. Tenofovir exposure was independently associated with an increased risk for three types of kidney events and did not appear to be reversible.
In the EUROSIDA cohort study on 6843 HIV-positive subjects with at least three serum creatinine measurements and corresponding body weight measurements from 2004 onwards, increasing exposure to tenofovir was associated with a higher incidence of CKD, as was true for indinavir and atazanavir, whereas the results for lopinavir/r were less clear.
The association with a boosted PI is important to guarantee adequate virological efficacy (although boosted atazanavir should be used only in the absence of other treatment options). Recent data show atazanavir to be potentially nephrotoxic, most likely due to tubulo-interstitial damage secondary to an indinavir-like cristalluria phenomenon.
Although there are no conclusive data regarding the toxicity of the new molecules (maraviroc and raltegravir), results achieved in published studies (MERIT, 004, SWITCHMRK) do not demonstrate renal toxicity.
A dual therapy study using lopinavir/r plus raltegravir (PROGRESS) was also seen to be kidney-friendly: eGFR reduction statistically significant.
The use of 3TC in dual therapy regimens is not currently supported by specific toxicity studies, however its use in these settings could be considered reasonable, given its widely accepted tolerability profile.
Monotherapy LDRs based on potent boosted PIs and low renal toxicity are a plausible option.
In the KITE study, the baseline mean CrCL was statistically significantly higher for LPV-r/RAL patients than sHAART patients (p=0.02). Among 28 subjects whose baseline sHAART regimen included TDF (n=17 in LPV-r/RAL and n=11 in sHAART),baseline adjusted CrCL (mean + SEM) in sHAART and LPV-r/RAL arms respectively, was 107+4 mL/min and 114+5 mL/min (week-2), 107+4 mL/min and 114+5 mL/min (week 24), and 111+6 mL/min and 117 + 7 mL/min (week-48), and did not significantly differ between arms.

Bone
HIV-infected patients had an increased risk of fracture compared to population controls. Moreover, the 10-year incidence of bone fractures was 3.6-fold higher in HCV co-infected patients.

Studies currently available concerning LDR (PROGRESS, MONET) show better performance on bone homeostasis in patients with backbone-sparing regimes, especially with regard to BMD and vitamin D.
The PROGRESS study at 96 weeks found a significantly reduction in BMD in patients taking LPV/r + RAL than those who received LPV/r + TDF/FTC.
Switching to raltegravir is associated with increases in total body BMD.
The SMART study showed a partial reversibility in bone damage in patients who stopped ARV.
Combination ARV therapies that include TDF have been shown to lead to an increased risk of inducing fracture.
TDF use, PI use, TNF-alpha activity and advanced HIV disease are associated with changes in bone turnover markers, highlighting the complicated interaction between ART, bone turnover, inflammation and immune status, which extend beyond the OPG/RANKL system.

Body changes
Pre-emptive or reactive switching from thymidine analogues (stavudine or zidovudine) to alternative nucleoside analogue agents or to a NRTI-sparing regimen was seen to cause modest gains in limb fat.
Cumulative exposure of thymidine analogue nucleoside reverse transcriptase inhibitors (stavudine and, to a lesser extent, zidovudine) is strongly associated with the development of lipoatrophy
A shift from lipoatrophy to lipohypertrophy is observed in the HAART era parallel to a reduction in the use of thymidine analogue nucleoside reverse transcriptase inhibitors and aging of the HIV population.
Switching from TDF/FTC to PI/r monotherapy is associated with an increase in limb fat.
At 96 weeks, a significant sparing of peripheral lipoatrophy was noted in the lopinavir/ritonavir monotherapy simplification strategy compared to an EFV-based triple regimen.
There are conflicting data on the role of the different PIs/r with regard to the benefit they have on lipoatrophy improvement.
In the ACTG 5142 study, lipoatrophy was less frequent for patients taking LPV/r than for patients taking EFV. In particular, EFV was associated with a 2.7 times higher risk of developing lipoatrophy when used with 2 nukes compared to LPV/r when used with 2 nukes. This difference was not affected by which nukes were used.
Progress study: 96 wks lipoatrophy recover.
ATV/r has been associated with greater central fat gain than EFV.
Switch from LPV/r regimens to ATV/r regimens in virologically suppressed HIV-infected adults, was associated with greater and statistically significant trunk fat, both subcutaneous and visceral.
The percentage of patients with an increase of 20% in total fat was 37.8% and 15.2% in the ATV/r and LPV/r groups, respectively (p¼0.018). In the ATV/r group, the increase in trunk fat (9.4%) was significantly higher than in peripheral fat (3.7%) (p¼0.007), leading to a significant increase in fat mass ratio (3.76%, p¼0.028), whereas no significant differences were found among LPV/r patients. CT scans showed that abdominal fat increase corresponded to both visceral (28%, p¼0.008) and subcutaneous fat (42%, p¼0.008).
Switching from a protease inhibitor to a NNRTI or abacavir did not lead to any improvement in lipohypertrophy
Lipodystrophy is uncommon for new ARV drugs (CCR5 and integrase inhibitors).

Mitochondrial toxicity
Mitochondrial toxicity drives long-term toxicities associated with cumulative exposure to NRTI, in particular with thymidine and adenosine analogue NRTIs, such as ZDV, d4T and ddI.
The clinical presentation of NRTI toxicity depends on the affected organs, including lipoatrophy, lactic acidosis, peripheral neuropathy, hepatic steatosis, myopathy, cardiomyopathy, pancreatitis, bone marrow suppression, and Fanconi syndrome.
Hepatic failure with refractory lactic acidosis is the most serious disease complication related to mitochondrial dysfunction. Stavudine, particularly when associated with didanosine, and less frequently zidovudine, has been associated with this clinical presentation.
Didanosine is involved in a rare, but serious, complication: non-cirrhotic portal hypertension.
Given the known association between NRTI (timidine analogues and d-drugs) and mitocondrial toxicities, it has been hypothesised that NRTI-sparing regimens could reduce mitochondrial dysfunction.

Pre-emptive or reactive switching from thymidine analogues (stavudine or zidovudine) to alternative nucleoside analogue agents or to an NRTI-sparing regimen has resulted in reduced risk or reverse mitochondrial toxicity.

Statements
- PI/r-based LDR are not indicated for the treatment of HIV patients with CVD or at high risk for CVD.
- PI/r-based LDR strategy may be considered in a subset of patients at risk for CVD not showing metabolic alteration under frequent monitoring (CIII).
- PI/r-based LDR can be an option in HIV/HCV co-infected patients with co-morbidities (BIII).
- PI/r-based LDR can be an option in HIV/HCV co-infected patients treated with IFN + RBV (BIII).
- In patients with non-alcoholic fatty liver disease (NAFLD) and co-morbidities contraindicating the use of NRTI, a PI/r-based LDR regimen could be considered (BIII).
- TDF/3TC, TDF/FTC, TDF and entecavir-sparing regimens are contraindicated in HBsAg positive or HBcAb and HBV-DNA positive patients (AII).
- A PI/r-based LDR strategy can be considered in the subset of patients with increased risk of or with overt kidney disease and:
  - TDF exposure especially in combination with PI/r (AII).
  - Co-morbidities or genetic predispositions (BII).
  - Patients with overt kidney disease (AII).
  - Patients with eGFR between 60-90 ml/min (BII).
  - Patients with unmodifiable risk factors (BII).
- A PI/r-based LDR strategy can be considered in the subset of patients at increased risk of osteoporosis or osteoporotic fractures and:
  - TDF exposure especially in combination with PI/r (AII).
  - Co-morbidities or genetic predispositions (BII).
  - Patients with osteoporosis (AII).
  - Patients with osteopenia (BII).
  - Patients with unmodifiable risk factors or with increased turnover markers (BII).
- PI/r-based LDRs could prevent worsening and partially revert lipoatrophy (AI).
- PI-based LDRs do not appear to reduce lipohypertrophy (BII).
- PI/r-based LDRs may prevent mitochondrial toxicity (AII).

Neurocognitive aspects

PI/r monotherapy should be able to suppress HIV replication in all body compartments, although not all PIs behave the same, since 2 subjects showed CNS viral escapes. In the MONOI study, of the 112 participants randomised to receive DRV/r BID, 2 developed neurological symptoms compared with none amongst the 113 patients randomised to continue with their current HAART. In these 2 patients, the CSF demonstrated elevated HIV-RNA levels, 330 and 580 cp/mL respectively, whereas plasma HIV-RNA levels were suppressed.

An LDR might be suboptimal in inhibiting CNS infection, due to low drug levels in the infected cells (potential low penetration through the blood-brain barrier of individual drugs). This could be of particular concern in patients with a history of HIV encephalitis, since this condition might be associated with the presence of a significant virus reservoir in brain macrophages.

However, a study evaluating neurocognitive impairment in patients before and after switching from first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) to second-line LPV/r-containing regimens (LPV/r-based monotherapy or TDF/3TC/LPV/r) showed a significant NCI improvement in both arms with a residual incidence of neurocognitive impairment after switching to LPV/r less than 7% and this rate did not differ with the study arms.

In a recent cross-sectional study in HIV-infected patients on LPV/r-HAART or LPV/r monotherapy, during at least 2 years, while maintaining plasmatic viral load <50 copies/mL, the proportion of patients with complete virological suppression in CSF (ultrasensitive HIV-1 RNA <1 copy/mL) was similar between LPV/r monotherapy and LPV-HAART groups. In addition, neurocognitive functioning proved mildly better (close to statistical significance) in patients on LPV/r monotherapy than in patients on LPV-HAART.

Darunavir CSF concentrations in patients taking the 800/100 once-daily or the 600/100 twice-daily dosage of the drug are different: recent data show that darunavir and ritonavir dosing not on-

ly significantly affects CSF concentrations, but also the extent of drug penetration into CSF in the once-daily dosage.

Statements

- Although PI/r monotherapy could favour a reduced HIV load in CSF, this strategy is not indicated for use in naïve patients, due to insufficient systemic efficacy (AI) and lack of evidence on the long-term risk of effective HIV suppression in CSF and risk of neurocognitive impairment (AIII). In naïve patients, when triple therapy is contraindicated (e.g. toxicities, RT resistance), an LDR based on dual therapy only can be considered (CII).
- In neuroasymptomatic patients who start cART, if an LDR dual regimen is indicated, combination should contain two drugs with high-ranking CNS penetration/effectiveness (CPE) at a CD4 level between 350 and 200 cells/mm3, (BIII) or <200 cells/mm^3 (AIII).
- In neuroasymptomatic HIV-patients showing virological suppression, a LDR regimen can be administered (BI). When PI/r monotherapy is used Lopinavir/r (400/100 BID)- and Darunavir/r (600/100 BID)-based LDR regimens are those offering the greatest potential for success for neuroprotection (BIII).
- PI/r monotherapy, for CNS protection, should be limited to patients without previous PI failures, who are highly compliant, with a viral suppression for >12 months and CD4+ nadir >100 cells/mm (AII).
- Neurological monitoring, plasma testing for resistance and drug concentration, and, where applicable, CSF examination for VL, resistance and drug concentration, is recommended when virological failure occurs during PI/r monotherapy (BII).
- In neuroasymptomatic patients with virological failure, LDR may be used exclusively in dual regimens, based on full activity by resistance/tropism tests (AII).
- For this statement, ANI patients are considered as neuroasymptomatic patients, because, at this point, there is inadequate evidence indicating that ANI would progress to symptomatic forms. LDR can be employed following the same recommendations as for asymptomatic patients (AIII). Special attention should be dedicated to the possibility of CSF escape (AII).
- LDRs should be avoided in patients who are neurologically symptomatic or have previously HIV-related symptomatic neurocognitive impairment (AII).

Patient-physician LDR communication needs

In recent years, the paternalistic model that historically characterised the relationship between physicians and their patients has fully evolved into a modern model in which the patient's role in his/her own medical care is more central than in the past. Patient involvement in this context has therefore become an increasingly important area of research in many chronic diseases.

Studies have shown that patients who state a greater involvement in their medical care are more satisfied with their physician, state a better understanding, reassurance, perceived control over their illness and experience improvements in their medical conditions. In particular, PLWH (People Living with HIV) are historically well-informed about treatment issues: the patient-physician relationship is one of the most important sources of information, but the Internet and PAGs (Patient Association Groups) are valuable alternatives commonly used by patients.

Therefore, exploring the specific contents of patient-physician communication when evaluating an LDR approach, is both an innovative field and an essential need, in that it must be added to the normal contents of standard HIV-1 communication.

Statements

There are common general issues, regardless of the setting in which an LDR approach is considered, that are highly recommended for discussion in a dedicated patient-physician meeting.

- Tailoring antiretroviral therapy and treatment of HIV-1 in a long-term perspective: modifying the regimen according to patient needs at certain times in his/her life, to be decided on according to clinical presentation and/or to prevent possible future clinical complications, as well as to meet patient needs as regards lifestyle. Changing treatment should not be considered a 'problem', but rather an 'opportunity' and 'smart management' of a life-lasting disease (AIII).
- Information on the LDR definition in HIV-1

and about the pros and cons of an 'unconventional strategy': exploring the reasons for considering LDR, also including scientific information, according to the individual patient's skills, and the necessary updates between a past and a present vision of HIV treatment management (AIII).
- Explaining the difference between "simplified HIV maintenance-suppression drug regimen" and "simplification". The use of a schematic simplification (i.e. fewer than 3 drugs) should be perceived as an important opportunity for achieving the maximum therapeutic result with the minimum therapeutic effort, by decreasing the drug pressure on the virus and stressing the advantage of taking less medication, even if this could mean 'taking more pills more times' (AI-II). For patients who are particularly concerned about pill burden but who are in favour of the LDR strategy, a co-formulated PI with a PK enhancer could also be considered (BIII).
- Dealing with patient stress regarding treatment switches: in some cases of current ARV regimens, both the application of an LDR maintenance strategy and the management of eventual virological failure in this setting do not imply a risk of new side-effects or toxicity (AIII). Reassuring the patient of possible consequences: in the event of virological failure, irreversible consequences are rare and 'specific strategies' for re-establishing undetectability are available; discussing the procedures with him/her (AIII).
- Evaluating the importance of adherence: optimal adherence should be the preliminary condition for considering LDR (AII). In any case, close monitoring of adherence is highly recommended (AI). Adherence support measures, such as reminders or pill boxes, could be suggested (BIII).
- Sharing the strategy by reaching an agreement: discussing it (according to the individual patient's skills), exploring the patient's motivation and assessing the patient's understanding as regards his/her situation – focussing particularly on specific populations (i.e. migrant people, prisoners, the elderly, drug-users) that could need tailored attention to facilitate the communication process. Scheduling regular feedback meetings could be recommended (AIII).
- Providing information on specific diagnostic tools/monitoring intensification: discussing with the patient all possible issues that could involve daily life, such as the need to intensify clinical controls, adherence assessments and blood draws for the monitoring of virological suppression (AIII).
- Reassuring the patient that the reason for choosing an LDR strategy is not based on cost-related issues (AIII). Some LDRs could also involve a reduction in the global drug cost: the issue of costs seldom arises during patient-physician meetings, but it might be suggested (if applicable) to mention the favourable impact of LDR on healthcare system costs (CI-II), accordingly on the patient-physician relationship. Discussion should be tailored depending on the patient's capacity to understand and share the importance of a global sense of responsibility on this issue (BIII).

PharmacoEconomics

Since the introduction of HAART therapies well-documented evidence has demonstrated that the predicted survival years for patients diagnosed with HIV-1 has continued to increase which has also resulted in an increase in health resource absorption.

In this setting, another important issue is the impact of long-term toxicity. Although no data or information regarding the economic issues relating to this field have been studied, this could change the absorption of resources and increase costs, particularly in terms of the economic need to diagnose and cure the corresponding complications. The possibility of reducing toxicity with the implementation of LDRs may also reduce the economic burden of these complications, thereby freeing up economic resources that could be used to treat a larger number of HIV-infected patients. Moreover, some LDRs regimens sensibly reduce the costs of prescribed drugs by definition.

All these considerations make it essential to examine potential LDRs, also evaluating the monetary impact and the sustainability of the implementation of this new treatment alternative in the third cART era.

Statements

- The reduction of the number of drugs administered to patients with the implementation of

an LDR strategy, for specific selected categories of HIV-positive subjects and for particular LDR regimens, could be a cost-effective perspective strategy that should be considered (BIII). More specific data are required.
– When standard therapies show reasonable similar efficacy in comparison with LDR, the economic criteria of resource optimisation should be taken into consideration in the context of simplification strategy (BIII). More specific data are required.

Final Remarks

Simplification of a suppressive triple antiretroviral therapy to LDR has demonstrated safety and efficacy in a high proportion of stable patients.
The key rationales behind regimen simplification are to improve the patient's quality of life and to maintain long-term compliance, without enhancing the risk of virological failure.
LDRs offer the potential advantages of a decreased risk or reversal of toxicities associated with the use of nucleoside analogue reverse transcriptase inhibitors (NRTIs). Furthermore, LDRs offer the advantage to maintain future active treatment options in a long perspective strategy for the management of HIV disease.
The use of high genetic barrier antiretroviral drugs (basically, PIs/r) in dual NRTIs-sparing regimens or in monotherapy regimens minimises the selection of drug-resistant HIV variants.

Due to the frequency of the citations in the text, the following references are displayed in alphabetical order

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