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FULL PAPERS

Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update 2015

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INTRODUCTION

This publication summarizes the latest updates to the 2014 version of the Italian Guidelines for the use of antiretroviral drugs. In particular, new recommendations were released concerning the following topics: optimal timing and drug combinations for starting combined antiretroviral therapy (cART), treatment optimization, and the use of new anti HCV drugs for the therapeutic management of HIV/HCV co-infected patients. Recommendations reported in the present update of the Italian Guidelines are based upon scientific evidence and expert opinion (*Table 1*).

This is a short version of the full text Italian Guidelines for the use of antiretroviral drugs and the diagnostic-clinical management of people with HIV-1 infection (HIV/AIDS Italian Expert Panel 2015, Antinori *et al.*, 2015c). By definition, this version should not be considered completely exhaustive with respect to the full text version of the Guidelines.

For a complete review of clinical and therapeutic relevant topics such as continuum of care, management of comorbidities, as well as populations (elderly, women, immigrants, children), conditions (drug and/or alcohol addiction, detention) and situations (transplants) requiring special attention we refer the reader to the extended version of the Guidelines. Similarly, while references cited herein refer only to the current update, a complete review of literature is available in the extended version of the Guidelines (HIV/AIDS Italian Expert Panel 2015).

WHEN TO START ANTIRETROVIRAL THERAPY

Following the recent publication of the two randomized clinical trials (RCT) START and TEMPRANO (INSIGHT START Study Group *et al.* 2015; TEMPRANO ANRS Study Group *et al.,* 2015), the degree of recommendation for initiation of cART in subjects with CD4 T cells counts higher than 500 cells/μl has been modified. Specifically, the results of these studies emphasize the positive impact of early therapy on patients' global health, and the importance of proposing antiretroviral therapy to all HIV infected individuals irrespective of their immune-virological status (Lazzarin *et al.,* 2015). Thus, this panel strongly recommends to initiate cART in all HIV infected adults regardless of their clinical status [AI].

Antiretroviral therapy has been shown to significantly reduce viral load in plasma and rectal mucosa, as detected by ultrasensitive assays, in all HIV infected patients, including elite controllers. Similarly, following cART initiation, the levels of immune activation markers and immune dysfunction significantly decrease in peripheral blood as well as in gut tissue. For these reasons, early initiation of cART is recommended also in elite controllers with the aim of reducing long term consequences of viral replication and chronic inflammation [BII].

Finally, prompt initiation of therapy is recommended also in pregnant women diagnosed in acute/recent infection,

Table 1 - *Rating scheme for degree of recommendation (a) and level of evidence (b).*

1a Degree of recommendation	
A	Highly recommended
B	Moderately recommended
C	Optional
1b Level of evidence	
Level I	The data are obtained from at least one controlled, randomized study with sufficient power or from a meta-analysis of controlled studies.
Level II	The data are collated from non-randomized studies or from cohort observational studies.
Level III	Recommendation based on case reviews or agreement among experts.

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Table 2 - *Recommendations for Initiation of cART in patients with PHI.*

Clinical condition	*CD4 T cell count*	*Recommendation for treatment*	*Degree of recommendation/ Level of evidence*	*Literature*
Asymptomatic/ Symptomatic	all values	always	[AII]	(Ananworanich *et al.* 2012; Brenner *et al.* 2007; Daar *et al.* 2008; Grijsen *et al.* 2012; Hatano *et al.* 2013; INSIGHT START Study Group *et al.* 2015; Kahn and Walker 1998; Le *et al.* 2013; Lockman and Creek 2009; Mehandru *et al.* 2006; Oxenius *et al.* 2000; Pilcher *et al.* 2004; Rosenberg *et al.* 2000; Saez-Cirion *et al.* 2013; Schacker *et al.* 1996; Spartac Trial Investigators *et al.* 2013; TEMPRANO ANRS Study Group *et al.* 2015)

in order to prevent possible perinatal transmission [AI].
New recommendations (including rates of recommendation, levels of evidence and relevant literature) for therapy initiation are listed in *Table 2* and *Table 3*. It is worth to note that treatment is always recommended [AI] in presence of opportunistic infections, although the timing for initiation of therapy can differ in relation to the specific characteristics of the ongoing opportunistic disease (for a more detailed review of this issue we refer the reader to the complete version of the Italian Guidelines; HIV/AIDS Italian Expert Panel 2015).

THERAPEUTIC REGIMENS IN NAÏVE PATIENTS

In naive patients receiving effective cART, complete virological suppression (decrease of plasma HIV RNA levels below the limit of detection of standard diagnostic tests) is achieved within 3-6 months from therapy initiation. Suppression of viral replication is associated with reduction of HIV related mortality and morbidity together with immunological recovery and reduction of the inflammatory state and of its associated complications. Moreover, suppression of viral replication has been associated to positive community effects such as a possible reverse of HIV epidemics due to the reduced risk of HIV transmission, and the de-stigmatization of people living with HIV. Thus, because of its direct and indirect effects on patients' life quality and its relevance to public health, rapid suppression of viral replication must be actively pursued in all patients.
The choice of a specific pharmacological treatment must be based on patients' individual needs. Several clinical and non-clinical factors play a role in determining treatment efficacy (*Table 4*) and they all need to be considered in order to identify the best first regimen for a given patient (Antinori *et al.,* 2015a).
The standard pharmacological treatment for HIV patients naïve to therapy usually includes a combination of different antiretroviral drugs into the therapeutic regimen.

Table 3 - *Recommendations for initiation of cART in patients with chronic infection.*

Clinical condition	*CD4 T cell count*	*Recommendation for treatment*	*Degree of recommendation/ Level of evidence*	*Literature*
Asymptomatic/ Symptomatic	All values	Always	[AI]	(INSIGHT START Study Group *et al*. 2015; TEMPRANO ANRS Study Group *et al*. 2015)

Table 4 - *Factors influencing the choice of the first regimen.*

Category	*Factors*
Drugs and drug combinations	Virological efficacy Immunological efficiency Compactness/convenience Toxicity and tolerability Potential drug-drug interaction Genetic barrier Extensive clinical use
Clinical practice or diagnosis	Presence of an AIDS defining conditions or other associated pathologies Plasma HIV RNA levels Presence of transmitted resistances HLA type (presence or absence of HLA-B*5701)
Non-clinical	Assessment of patient's willingness and readiness to start treatment Population specific characteristics Particular conditions

For a more detailed description of the single factors influencing the choice of the first regimen we refer the reader to the last edition of the Italian guidelines for the treatment of HIV infected patients.

Clinical trials, which provide fundamental information for the choice of therapy, are usually based on comparison of different regimens rather than single drugs. Nevertheless, for the choice of an appropriate drug combination is mandatory to consider also the information concerning the properties of the single molecules included in the therapy. Current HIV guidelines agree to recommend the use of an antiretroviral regimen effective in presence of high viral load (HIV RNA >100.000 copies/ml) for treatment initiation in acute and recent infections [AII]. Despite the lack of evidences deriving from clinical trials, in patient with extremely high baseline viral loads (HIV RNA >500.000 copies/ml), infection diseases specialists might favour regimens including integrase inhibitors, which are characterized by a stronger and faster activity [CII] compared to other classes of drugs (Andreoni *et al.,* 2015). Given the fact that current cART needs to be taken lifelong, it seems appropriate to implement the first regimen according to a stepwise strategy, in which a therapeutic combination providing a strong and rapid reduction of viral load (in order to achieve the goals resulting from reduction of viral replication), is followed by an optimized regimen, tailored to maintain viral suppression while better matching the present and future needs of the patient (see Treatment Optimization).

CLASSIFICATION AND DEGREE OF RECOMMENDATION OF CART REGIMENS FOR THE TREATMENT OF ANTIRETROVIRAL (ARV)-NAIVE PATIENTS

Recommended regimen options (for all conditions) (Table 5a) [A]

The present document recommends seven ARV regimens, six based on integrase strand transfer inhibitors (INSTIs) and one based on non-nucleoside reverse transcriptase inhibitors (NNRTI).

Table 5a - *Antiretroviral regimens recommended for starting cART.*

Regimen	*Degree of recommendation/ Literature Level of evidence*	
Recommended regimen options (for all conditions)		
TDF/FTC + RAL	[AI]	(Lennox et al. 2009; Lennox et al. 2014; Raffi *et al.* 2013a; Raffi *et al.* 2013b; Rockstroh *et al.* 2013)
TDF/FTC/EVG/COBI	[AI]	(Clumeck *et al.* 2014; DeJesus *et al.* 2012; Sax *et al.* 2012; Squires *et al.* 2015; Wohl *et al.* 2014)
TAF/FTC/EVG/COBI	[AI]	(Sax *et al.* 2015)
TDF/FTC + DTG	[AI]	(Clotet *et al.* 2014; Raffi *et al.* 2013a; Raffi *et al.* 2013b)
ABC/3TC + DTG	[AI]	(Clotet *et al.* 2014; Raffi *et al.* 2013a; Raffi *et al.* 2013b; Walmsley *et al.* 2013)
ABC/3TC/DTG	[AI]	(Clotet *et al.* 2014; Raffi *et al.* 2013a; Raffi *et al.* 2013b; Walmsley *et al.* 2013; Weller *et al.* 2014)
TDF/FTC/RPV (for patients with HIV-RNA <100.000 copies/ml and T CD4+ count >200 cells/µl)	[AI]	(Cohen *et al.* 2012; Molina *et al.* 2011) (Cohen *et al.* 2013a; Cohen *et al.* 2014)
Recommended regimen options (for particular conditions)		
TDF/FTC+ATV+r or TDF/FTC+DRV+r (recommended in individuals with uncertain adherence or in patients who need to begin treatment before resistance testing results are available, as well for therapy initiation in pregnant patients)	[AII]	(Clotet *et al.* 2014; Clumeck *et al.* 2014; Daar *et al.* 2011; DeJesus *et al.* 2012; Gallant *et al.* 2013; Lennox *et al.* 2014; Mills *et al.* 2015a; Molina *et al.* 2010; Orkin *et al.* 2013; Ortiz *et al.* 2008; Soriano *et al.* 2011)
TDF/FTC+ATV/COBI or TDF/FTC+DRV/COBI (recommended in individuals with uncertain adherence or in patients who need to begin treatment before resistance testing results are available)	[AII]	(Gallant *et al.* 2015; Tashima *et al.* 2014)

NNRTI based regimens are not recommended in presence of mutations conferring resistance to NRTI and NNRTI.
Because of the possible occurrence of hypersensitivity reactions (HSR), ABC is not recommended in subjects harbouring the HLA allele B*5701.
COBI is not recommended in patients with impaired renal function (GFR <70 ml/min/1.73 m^2). Follow-up data about tubular toxicity are limited. The combination EVG/COBI/FTC/TAF is a therapy option for patients with eGFR >50 ml/min.
Regimens including TDF/FTC + ATV/r, ATV/COBI, DRV/r, or DRV/COBI are recommend [AII] only for the above mentioned conditions. In all the other cases, they should be considered as alternative regimens [BI].
DRV/r dosage is 800 /100 mg once a day.
Risk of hyperbilirubinemia and hyperbilirubinemia-associated adverse effects needs to be considered before prescribing ATV/r and ATV/COBI.
The regimen TDF/FTC/RPV is not licensed for patients with HIV-1 plasma RNA >100000 copies/ml.Regimens including COBI are not recommended for treatment of pregnant patients.
"/" = co-formulated; "+" = not co-formulated.

The only recommended NNRTI-base regimen TDF/FTC/EFV is indicated for ART initiation only in patients with HIV-RNA <100.000 copies/ml and CD4 T cell count >200 cell/μL, according to regulatory limitations approved. In all these recommended regimens, the backbone nucleoside consists of a combination of FTC and TDF or tenofivir alafenamide (TAF), except for the combination of ABC and 3TC, which is is recommended when associated to the INSTI dolutegravir. Four out these seven regimens are available as single tablet regimen (STR). All these recommended regimen options meet all the following criteria:

- Proven efficacy in RCT with sufficient potency (quality, numerosity, adequacy of control groups). In particular, the proposed antiretroviral regimen must demonstrate non-inferiority over a recommended regimen and meet at least one of the following conditions:
- Demonstrated superiority compared to at least one alternative regimen,
- Better tolerability and non inferiority compared to a recommended regimen;
- Favourable acceptability, tolerability, and safety profiles;
- Well established clinical use demonstrated by the number and duration of clinical trials, by the data deriving from observational studies, or by the extensive use in clinical practice after their introduction to the market.

Recommended regimen options for particular conditions (Table 5a) [A]

Four different boosted-protease inhibitors (PI) are now recommended in particular conditions (such as uncertain adherence con in patients who need to begin treatment before resistance testing results are available, or for therapy initiation in pregnant women), including boosted ATV or DRV (enhanced by low-dose RTV or COBI), both combined to TDF/FTC as backbone nucleoside. All these regimens, although not fulfilling all the criteria for recommended regimens, can be considered as preferable therapeutic options because of proven benefits in terms of efficacy, genetic barrier, tolerability, and safety.

Alternative regimen options (Table 5b) [B]

These regimens partially meet the criteria for recommendation because of the following reasons:

- Regimen efficacy is supported by incomplete evidences;
- Suboptimal acceptability, tolerability, and safety profiles;
- Proven inferiority to one of the recommended regimens.

Optional regimen options (Table 5c) [C]

These regimens show:

- Insufficient or contrasting evidences supporting regimen efficacy;

Table 5b - *Alternative drugs combinations for first regimens.*

Regimen	*Degree of recommendation/ Level of evidence*	*Literature*
TDF/FTC+EFV	[BI]	(Arribas *et al.* 2008; Carey 2014; Cohen *et al.* 2013a; Cohen *et al.* 2014; Daar *et al.* 2011; DeJesus *et al.* 2004; Gallant *et al.* 2006; Lennox *et al.* 2009; Molina *et al.* 2011; Nelson *et al.* 2013; Post *et al.* 2010; Riddler *et al.* 2008; Rockstroh *et al.* 2013; Sax *et al.* 2012; Sax *et al.* 2009; van Leth *et al.* 2004; Walmsley *et al.* 2013; Wohl *et al.* 2014)
ABC/3TC+EFV (recommended if plasma HIV-1 RNA <100000 copies/ml)	[BI]	(Daar *et al.* 2011; Post *et al.* 2010; Sax *et al.* 2011; Sax *et al.* 2009)
ABC/3TC+ATV+r (recommended if plasma HIV-1 RNA <100000 copies/ml)	[BI]	(Daar *et al.* 2011; Sax *et al.* 2011; Sax *et al.* 2009)
ABC/3TC+ATV/COBI (recommended if plasma HIV-1 RNA <100000 copies/ml)	[BIII]	(Daar *et al.* 2011; Ramanathan *et al.* 2009; Sax *et al.* 2011; Sax *et al.* 2009)
ABC/3TC+DRV+r	[BII]	(Clotet *et al.* 2014)
ABC/3TC+DRV/COBI	[BIII]	(Clotet *et al.* 2014; Kakuda *et al.* 2014)
ABC/3TC+RAL	[BII]	(Raffi *et al.* 2013a)
DRV+r + RAL (recommended if CD4 T cell count >200 cells/μl; caution must be used when prescribing this combination in patients with HIV RNA viral load >100.000 copies/ml)	[BI]	(Raffi *et al.* 2014)

NNRTI based regimens are not recommended in presence of mutations conferring resistance to NRTI and NNRTI.
The standard dosage of EFV is 600 mg/once a day. The *off label* dosage of 400 mg once a day proved to be not inferior to standard dosage if prescribed in association with TDF/FTC.
Because of the possible occurrence of hypersensitivity reactions (HSR), ABC is not recommended in subjects harbouring the HLA allele B*5701.
DRV/r dosage is 800 /100mg once a day.
Risk of hyperbilirubinemia and hyperbilirubinemia-associated adverse effects needs to be considered before prescribing ATV/r and ATV/COBI. Use of COBI is contraindicated in patients with impaired renal function (GFR <70 ml/min/1.73 m^2). Follow up data concerning tubular toxicity are limited.
Regimens including COBI are not recommended for treatment of pregnant patients.
"/" = co-formulated; "+"= not co-formulated.

Table 5c - *Optional drugs combinations for first regimens.*

Regimen	*Degree of recommendation/ Level of evidence*	*Literature*
TDF+3TC+EFV	[CI]	(Gallant *et al.* 2004)
TDF/FTC+NVP	[CI]	(Cain *et al.* 2012; Soriano *et al.* 2011; van Leth *et al.* 2004)
ABC/3TC+RPV (recommended if plasma HIV-1 RNA <100000 copies/ml)	[CII]	(Cohen *et al.* 2011; Cohen *et al.* 2013b; Molina *et al.* 2014; Nelson *et al.* 2013)
TDF/FTC+LPV/r	[CI]	(Smith *et al.* 2009)
ABC/3TC+LPV/r	[CI]	(Smith *et al.* 2009)
LPV/r + 3TC	[CI]	(Cahn *et al.* 2014; Rolon 2015)
LPV/r + RAL	[CI]	(Reynes *et al.* 2013)

NNRTI based regimens are not recommended in presence of mutations conferring resistance to NRTI and NNRTI.
Due to the high risk of developing HSR, ABC is not recommended in subject harbouring the HLA allele B*5701.
NVP is not recommended for use in women with a CD4 T cell count >250 cells/µl or men with a CD4 T cell count >400 cells/µl. NVP is initiated at half of the usual dose (400 mg/day) in the first 14 days of treatment using extended-release tablets (one pill once a day).
"/" = co-formulated; "+"= not co-formulated.

- Suboptimal acceptability, tolerability, and safety profiles.

Optional regimens are recommended only if the patient does not tolerate or is unable to take recommended or alternative regimens (due to resistance, toxicity or intolerance). For pro and cons of single drugs and drug combinations including tolerability and toxicity, pharmacological interactions, formulations, posology, we refer the reader to the complete version of the Italian Guidelines (HIV/AIDS Italian Expert Panel 2015).

TREATMENT OPTIMIZATION

Drugs reduction

The goal of this treatment scheme, also known as Less Drug Regimen (LDR), is to reduce the number of antiretroviral drugs included in a given regimen by applying a two-phase induction maintenance therapeutic strategy (Marcotullio *et al.,* 2014). In the first phase, viral suppression is achieved through a standard triple antiretroviral regimen. Then, once plasma viral load is not detectable anymore and immunoreconstituition is taking place (at least 6 months after achieving viral suppression), treatment could be switched to a LDR. The aim of this therapeutic approach is to limit or prevent long term toxicities, increase tolerability and reduce pharmacological interactions, while maintaining virological control. Of note, benefit in terms of reduction of possible drug-drug interactions is of particular interest given the aging of the HIV population and the use of concomitant medications for management of comorbid diseases.
The following paragraphs describe the current therapeutic scenario for switching to LDR in cART treated patients with viremia below the detection limit. To give a broaden overview of all the possible therapeutic strategies, drug combinations are described regardless of the specific indications provided in the technical datasheets.

Dual therapy (Table 6)

Dual therapy regimens were developed with the aim of excluding NRTIs from the therapeutic combinations, since these drugs show higher long-term toxicities. However, due to the fact that 3TC and FTC are characterized by better toxicity profiles, combinations including a ritonavir boosted protease inhibitors (PI/r) in combination with 3TC and FTC have also been evaluated. In view of the results of RCTs which reached their primary endpoint, the combination of ATV/r + 3TC might be recommended [AI*/BI; *in patients switching from ATV/r, otherwise BI] in patients experiencing NRTI associated toxicity, or recommended [BI] to prevent the occurrence of toxicity associated to NRTI other than 3TC or FTC.
Combinations including darunavir DRV/r + 3TC or FTC might be moderately recommended [BII] in presence of NRTI associated toxicity and considered as optional [CI] to prevent the occurrence of toxicity associated to NRTI other than 3TC or FTC. The combination of LPV/r + 3TC should be considered as optional in presence of or to prevent NRTI toxicity [CI].
The optimization schemes LPV/r + 3TC and ATV/r + 3TC proved to be non inferior to the continuation of a standard regimen in two different RCTs (Arribas *et al.,* 2015; Perez-Molina *et al.,* 2015). In addition, a randomized trial the combination of ATV/r + 3TC was demonstrated as superior compared to ATV/r + 2NRTIs at 48 weeks (Di Giambenedetto *et al.,* 2015). However, caution must be taken when switching to LPV/r given the increased pill burden and the twice a day administration scheme together with the potential risks of long term toxicities.
The combination of DRV/r + 3TC or FTC has been evaluated only in non controlled studies, where it showed sufficient evidence of effectiveness (Borghetti *et al.,* 2014; Gianotti *et al.,* 2014a). Switch from triple regimens to ATV/r + RAL was proven to be virologically inferior to continuation of standard therapeutic regimen and thus should be avoided (van Lunzen *et al.,* 2014; van Lunzen *et al.,* 2016).
Finally, studies analyzing double regimens which do not include the use of PI/r have limited consistency or gave discouraging results in terms of efficacy; therefore these regimens are currently not recommended.

Boosted protease inhibitors monotherapy (Table 7)

Improvement of toxicity profile together with reduction of

Table 6 - *Summary of rationale/advantages/disadvantages of dual therapy for treatment optimization.*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*Literature*
From a triple drug combination to a PI/r + NNRTI regimen	Reduce/ Prevent NRTI associated toxicity.	Proven virological efficacy in subjects not eligible for simplification to monotherapy	Development of resistance towards the newly introduced therapeutic class following virological failure. NNRTI associated toxicity; first generation NNRTI associated toxicity	[CI]	(Maggiolo *et al.* 2015; Negredo *et al.* 2009; Negredo *et al.* 2005)
From a triple drug combination to DRV/r or LPV/r + RAL	Reduce/ Prevent NRTI associated toxicity.	Proven virological efficacy in subjects not eligible for simplification to monotherapy	Increased virological failure, development of resistance towards integrase inhibitors; metabolic profile impairment	[BI] in patients experiencing toxicity induced by NRTIs or [CI] as a preventive measure	(Madeddu *et al.* 2014; Nishijima *et al.* 2013; Ofotokun *et al.* 2014)
From a triple drug combination to LPV/r + 3TC	Reduce/ Prevent NRTI associated toxicity	Virological efficacy non inferior to triple combination.	Increased PI associated toxicity; increased pill burden except for patients switching from a 2NRTI + LPV/r regimens; gastrointestinal side effects; long-term increase in cardiovascular risk	[CI]	(Arribas *et al.* 2015)
From a triple drug combination to ATV/r + 3TC	Reduce/ Prevent NRTI associated toxicity	Virological efficacy non inferior to triple combination. Superior virological efficacy if switching from ATV/r + TDF/FTC	Possible increase of PI associated toxicity	[AI*/BI] in patients experiencing toxicity induced by NRTIs other than except 3TC/FTC or [BI] as a preventive measure **in patients switching from ATV/r, otherwise BI	(Di Giambenedetto *et al.* 2013; Di Giambenedetto *et al.* 2015; Perez-Molina *et al.* 2015)
From a triple drug combination to DRV/r + 3TC or FTC	Reduce/ Prevent NRTI associated toxicity	Proven virological efficacy in subjects not eligible for simplification to monotherapy	Possible increase of PI associated toxicity. Data from controlled clinical studies are lacking	[BII] in patients experiencing toxicity induced by NRTIs other than except 3TC/FTC or [CII] as a preventive measure	(Borghetti *et al.* 2014; Gianotti *et al.* 2014a)

treatment costs are the main advantages supporting the switch to boosted PI monotherapy in suppressed patients (Restelli *et al.,* 2014). Consistently, several studies have evaluated the switch from a standard therapeutic regimen to a monotherapy consisting of a PI/r. The PIVOT study evaluated the performances of monotherapy with PI/r compared to the conventional triple therapy; primary endpoint was loss of future treatment options based on development of drug resistance. After 3.5 years of follow-up this study indicates that monotherapy with PI/r is associated with 35% risk of virological failure (*vs* 3% of patients in triple treatment arm), does not induce clinical events, promotes a slight reduction of grade 3-4 adverse events (46% *vs* 55%, p=0,04), does not reduce the range of therapeutic options available for future switching, and has a favourable cost-effect profile.

A recent meta-analysis evaluating efficacy of DRV/r or LPV/r in several RCTs (n=1553) estimated a -7% differential difference (95% CI:-11% -4%) for the occurrence of virological failure between patients switching to monotherapy with PI/r and patients maintaining standard triple therapy (reintroduction of NRTI backbone was considered as virological failure). If return to previous regimens was not considered as failure, the estimated difference between the two arms was 0% (95%CI -3% +3%).

The only RCT which evaluated monotherapy with ATV/r (MODAT) was interrupted due to virological inferiority at 48 weeks compared to triple therapy. Similarly, the prolonged 96 week analysis did not demonstrate non-inferiority (efficacy: 64% ATV/r monotherapy vs 63% ATV/r + 2NRTI, difference +1.3%; 95% CI: -17.5%,-20.5%) (Spagnuolo *et al.* 2014).

Identification of variables associated with virological failure after switch to PI/r monotherapy is of interest in view of their possible application as predictors of efficacy after treatment change in switching strategies. Several variables, including low nadir CD4 T cell count, low therapy adherence, as well as limited duration of either the previous antiretroviral treatment or the viral suppression were all associated with an increased risk of failure in RCTs, observational studies and meta-analysis. Among these variables, nadir CD4 T cell count proved to be the most accurate parameter predicting virological failure. Increased risk of failure was associated with nadir CD4 T cell counts

Table 7 - *Summary of rationale/advantages/disadvantages of monotherapy for treatment optimization.*

Class of optimization	*Aims*	*Potential disadvantages*	*Degree of recommendation/Level of evidence*	*Literature*
From dual or triple therapy to LPV/r 400/100 mg twice a day	Reduce/Prevent NRTI associated toxicity	Increase pill burden except for patients coming from a LPV/r + 2NRTI regimen; adverse metabolic and gastroenteric events; increased long-term cardiovascular risk; lower virological efficacy; unclear results concerning virological efficacy in HIV sanctuaries; contraindicated in HBsAg positive patients	*et al.*	(Arribas *et al.* 2014a; Arribas *et al.* 2009; Bierman *et al.* 2009; Cahn *et al.* 2011b; Cameron *et al.* 2008; d'Arminio Monforte *et al.* 2014; Gianotti *et al.* 2014b; Gutmann *et al.* 2010; Paton *et al.* 2015; Pinnetti *et al.* 2014; Pulido *et al.* 2009)
From dual or triple therapy to DRV/r 800/100 mg once a day	Reduce/Prevent NRTI associated toxicity	Reduced virological efficacy (non inferior in patients with nadir CD4 T cell counts >200 cells/µl); contraindicated in HBsAg positive patients	[BI]] in patients experiencing toxicity induced by NRTIs or [CI] as a preventive measure	(Antinori *et al.* 2015b; Arribas *et al.* 2014a; Arribas *et al.* 2012; Bierman *et al.*2009; Geretti *et al.* 2013; Paton *et al.* 2015; Pinnetti *et al.* 2014; Valantin *et al.* 2012)
From dual or triple therapy to ATV/r 300/100 mg once a day	Reduce/Prevent NRTI associated toxicity	Reduced virological efficiency, in particular in HCV co-infected patients with baseline plasma HIV RNA >100.000 copies/ml; contraindicated in HBsAg positive patients	[CI] in patients experiencing toxicity induced by NRTIs. Not recommended as preventive measure	(Karlstrom *et al.* 2007; Spagnuolo *et al.* 2014; Swindells *et al.* 2006)

<100 cells/µl with LPV/r monotherapy, and to nadir CD4 T cell counts <200 cells/µl with LPV/r and DRV/r monotherapy. These observations support the application of a threshold of a nadir CD4 T cell count above 200 cells/µl to select HIV patients eligible for DRV/r or LPV/r monotherapy.
Concomitant HCV infection was suggested as a factor associated to virological failure during monotherapy by the MODAT and MONET studies, which evaluated the effect of switch to monotherapy with ATV/r and DRV/r, respectively. However, other studies based on DRV/r monotherapy such as the MONOI, PROTEA and PRIMO trials, as well as the studies including LPV/r, all failed to confirm this association and do not support the use of HIV/HCV coinfection as a predictor for PI/r monotherapy response. While waiting for more consistent data, it is advisable not to consider monotherapy with PI/r a strategy with a sufficient efficacy and safety in HIV/HCV co-infected patients.
In the MONOI and MONET studies, other additional factors able to predict virological failure of DRV/r monotherapy were identified, such as HIV viremia (HIV-RNA >1 copies/ml or >5 copies/ml) and HIV DNA levels at baseline. Increase in viral replication in cerebrospinal fluid (CSF) was sporadically reported in some patients enrolled in MOST, MONOI and MONET studies, leading to the hypothesis of a possible association between PI/r monotherapy and increasing risk of HIV replication in the CSF and neurocognitive impairment. However, in the PROTEA trial, none of patients with a CD4 nadir >200 cell/µL showed signs of HIV replication in CSF. Moreover, the analysis of the tree RCTs in which neurocognitive assessment was included in the trial evaluation scheme (PIVOT, PROTEA and MODAT), did not confirm the existence of an increased risk of neurocognitive impairment during PI/r monotherapy.
In light of the above mentioned studies, switch to DRV/r monotherapy can be moderately recommended in presence of NRTI associated toxicity [BI] and can represent an acceptable option to prevent NRTI associated toxicity [CI] in selected patients treated with PI, who have no history of virological failure to PI, no PI resistance associated mutations, suppressed viremia (viral load below 50 copies/ml) for at least 12 months, a nadir CD4 T cell count >200 cells/µl, and have no previous history of central nervous system associated adverse events.
Viral load monitoring every 3 months for the early identification of possible failures, and implementation of periodic strategies to monitor patient adherence [AIII] are generally recommended in patient undergoing monotherapy treatment with protease inhibitors. In case of virological rebound (two consecutive values higher than 50 copies/ml) a resistance test, performed on plasma HIV RNA[AIII] and proviral DNA [CIII], followed by resumption of triple therapy [AIII] are recommended.

Pill burden reduction (Table 8)

Different therapeutic approaches have been developed in order to reduce regimen complexity and promote adherence including once daily regimens, fixed dose combinations (FDC), and single tablet regimens.
FDC are combinations of two or more active drugs in a fixed ratio of doses which are preferred over non-standardized combinations. FDC may be administered as single products given concurrently or coformulated in one table, such as in STRs. cART adherence might be increased using regimens which involve a pill burden reduction by FDC or STR, and daily intake (QD) of medications (Maserati *et al.,* 2014).
Switching from PI to a different antiretroviral class (NNR-

Table 8 - *Summary of rationale/advantages/disadvantages of regimens with reduced doses/administration (including FDC and STR).*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*Literature*
From NVP + 2 NRTI to TDF/FTC/ RPV-FDC(a)	Improve adherence		Slight reduction of eGFR (uncertain clinical relevance)	[BII]	(Allavena *et al.* 2014; Gianotti *et al.* 2015; Mora-Peris *et al.* 2014)
From EFV + 2NRTI to TDF/ FTC/RPV FDC (b)	Reduce/prevent toxicity	Lower metabolic impact and improvement of EFV associated neurological symptoms	Slight reduction of eGFR (uncertain clinical relevance for RVP)	[BII]	(Cazanave *et al.* 2015; Gianotti *et al.* 2015; Mills *et al.* 2013)
From NNRTI to EVG/COBI/FTC/ TDF FDC (c)	Reduce/prevent toxicity	Lower incidence of CNS adverse events; slight improvement of metabolic profile	Slight reduction of eGFR (uncertain clinical relevance)	[AI]	(Mills *et al.* 2015b; Pozniak *et al.* 2014)
From PI/r to EFV (d)	Reduce/prevent toxicity	Available in co-formulation; lower incidence of gastrointestinal adverse effects	Increased incidence of adverse events, in particular of those targeting CNS; lower genetic barrier	[AI]	(Dejesus *et al.* 2009; Martinez *et al.* 2007)
From PI/r to NVP (d)	Reduce/prevent toxicity	Lower incidence of gastrointestinal adverse effects; lower metabolic impact	Short-term skin and liver toxicity: lower genetic barrier	[AI]	(Llibre et al. 2015; Martinez *et al.* 2007)
From PI/r to TDF/ FTC/RPV FDC (e)	Reduce/prevent toxicity.	Lower incidence of gastrointestinal adverse effects; lower metabolic impact	Lower genetic barrier	[AI]	(Gianotti *et al.* 2015; Palella *et al.* 2014)
From PI/r to RAL (f)	Reduce/prevent toxicity	Lower incidence of gastrointestinal adverse effects; lower metabolic impact	Lower genetic barrier; non inferiority was not reached in one of the studies; twice a day regimen; not recommended in presence of previous failure to NRTI; therapy initiation is recommended at least 6 weeks after achieving virological suppression	[BI]	(Curran *et al.* 2012; Eron *et al.* 2010; Martinez *et al.* 2010)
From PI/r to EVG/ COBI/FTC/TDF FDC (g)	Reduce/prevent toxicity.	Improved virological suppression; lower incidence of adverse effects; increased patient satisfaction	Lower genetic barrier	[AI]	(Arribas *et al.* 2014b; Gathe *et al.* 2015)
From all regimens to DTG/ABC/3TC FDC (h)	Reduce/prevent toxicity.	Increased patient satisfaction	Cardiovascular toxicity derived from the use of ABC cannot be ruled out; Increased number of adverse events	[BI]	(Trottier *et al.* 2015)
Da EFV 600 a EFV 300 mg (i)	Reduce/prevent toxicity.	Reduced neurological toxicity	Potential increase in the risk of virological failure	[CIII]	(Yang *et al.* 2014)

From a fixed combination EFV/FTC/TDF once a day to a fixed combination EFV/FTC/TDF once every other day(l)	Reduce/prevent toxicity.	Reduced neurological toxicity.	Potential increase in the risk of virological failure	[CI]	(Nicastri *et al.* 2015)
From LPV/r to ATV/r or DRV/r once day (m)	Reduce/prevent toxicity.	Lower impact on lipid metabolism, reduced pill burden	Co-formulation with RTV is not available; ATV increases the risk of hyperbilirubinemia	[AI]	(Gatell *et al.* 2007; Mallolas *et al.* 2009; Ucciferri *et al.* 2013)
From DRV/r twice a day to DRV/r once a day (n)	Therapy simplification	Lower impact on lipid metabolism reducedpill burden.	Contraindicated in presence of resistance to DRV/r; preferable if no resistance to DRV/r is detected (reduce therapy cost)	[AI]	(Cahn *et al.* 2011a)
From ATV/r+FTC/TDF to EVG/COBI/FTC/TAF FDC (o)	Therapy simplification, Reduce/prevent toxicity	Higher virological success, reduced adverse effects; reduction of proteinuria; improvement of BMD	Slight impairment of lipid profile (long-term clinical implications need to be assessed)	[AI]	(Mills *et al.* 2015c)

(a) A single centre open-label study demonstrated maintenance of virological suppression without any virological failure at week 24 in 29 out of 32 patient who switched from TDV/FTC + NVP to TDV/FTC/RPV. Additional studies have confirmed the absence of virological failure after switch.
(b) Although RCTs are missing, observational studies showed a low risk of virological failure in virologically suppressed patients switching to RPV/FTC/TDF STR
(c) Virological non-inferiority (93% vs 88%) at week 48 was demonstrated in a RCT enrolling 434 patients switching to STR containing EVG/COBI/FTC/TDF. The arm undergoing therapy simplifications showed lower incidence of SNC disorders, increased eGFR, and reduced metabolic impact compared with the control arm (NNRTI based therapy).
(d) The NEFA study evaluated the efficacy of NVP, EFV or ABC as a substitute for a PI in a group of 498 patients. Switching to EGV or NVP was more effective in maintaining virological suppression, however discontinuation due to adverse events was more frequent with NNRTIs. In a Spanish study including 341 patients, simplification to NVP from either EFV or PI has shown low incidence of virological and therapeutic failures as well as low occurrence of long term toxicities.
(e) In the SPIRIT study, 476 virologically suppressed HIV patients were randomized (2:1) to switch to TDV/FTC/RPV immediately or at week 24. Non inferiority of the simplification from PI to RPV was demonstrated at 24 weeks together with a slight increase of eGFR and in an improvement of lipid profile. Additional observational studies failed to identify significant risk of virological failure in patients with no history of previous resistance or risks of toxicity.
(f) The switch from LPV/r to RAL in virologically suppressed patients proved to be not inferior to continuation of therapy in RCT evaluating (SPIRAL). The factors mainly associated with virological failure were previous failures and thus, presumably, the presence of mutations conferring resistance to NRTI. A second RCT has shown virological non-inferiority, likely because of a longer period of suppression before the switch (at least six months). Both studies have shown a favourable impact on lipid profile, furthermore in SPIRAL study the switch to RAL significantly reduced statin consumption and improved bone mineral density.
(g) A RCT evaluating the effects of therapeutic simplification to a STR including EVG/C≤OBI/FTC/TDF showed superiority in viral suppression at week 48 compared to control group (antiretroviral therapy based on PI) (94% vs 87%). Moreover, patients included in the simplification arm showed a significant improvement of life quality and reduced incidence of gastrointestinal adverse effects.
(h) In a RCT which enrolled 551 patients, the simplification to a STR including DTG/ABC/3TC proved to be non inferior to continuing the previous therapeutic regimen in terms of virological suppression at 48 weeks. Moreover, patient satisfaction scores were higher in the treatment arm, despite a higher number of adverse events leading to treatment interruption.
(i) Open-label studies showed successful EFV dosage reduction guided by therapeutic drug monitoring; in particular, in a cohort of 111 patients in Taiwan, short-term virological suppression was fully maintained after reducing EFV from 600 to 300 mg/day.
(l) Virologically suppressed patients treated with EFV/FTC/TDF were randomized to continue the previous regimen administration scheme or to switch to a four times per week administration, with text message reminders to increase adherence. This pilot study showed no change in the risk of virological failure at week 48, although with no reduction of toxicity.
(m) The SWAN study evaluated the switch from PI to ATV or ATV/r + TDF, the ATAZPI study evaluated the switch from LPV/r to ATV/r, and the ARIES study evaluated the switch from ATV/r +ABC/3TC to ATV+ABC/3TC. The switch from LPV/r to DRV/r has been evaluated only in one not controlled study including 13 patients whose rationale and expected results have been elaborated on the basis of the studies comparing LPV/r and DRV/r regimens in naïve patients. In general, in studies evaluating the switch from LPV/r to another PI/r, patient maintained virological suppression and regimens, globally, showed increased tolerability (although switch to a new antiretroviral drug is associated to the risk of developing a new specific toxicity).
(n) In treated patients showing no resistance to DRV, the use of DRV/r 800/100 mg once a day proved to be not inferior and associated to a lower impact on lipid metabolism compared to the use of DRV/r 600/100 mg twice a day (ODIN study). Therefore, switch from DRV/r 600/100 mg twice a day to DRV/r 800/100 mg once a day is recommended, provided the absence of mutations associated with DRV resistance in the previous resistance tests.
(o) The GS-109 study (RCT including 601 patients) demonstrated a superior virological success at week 48, improvement of bone mineralization and kidney and tubular functionality together with a slight impairment of the lipid profile whose long term clinical implications need to be assessed.

TI or INSTI), i.e. from a regimen with a very high genetic barrier to a regimen with a lower genetic barrier, is recommended to improve therapy tolerability. It must be noted that this therapeutic choice is appropriate only for patients who have never experienced virological failure, have never been exposed to suboptimal concentrations of NRTIs, and do not present mutation associated with NRTI resistance (and NNRTI if the switch involves this class of drugs) [AI].

Moreover, a minimum of 6 months of virological suppression is required to switch to a regimen including RAL. Concerning the switch from a PI/r- based regimen to STR of EVG/COBI/FTC/TDF or EVG/COBIFTC/TAF, a higher efficacy at 48 weeks compared to PI/r-continuing control arm has been proven.

Finally, while data from RCTs are available to support the switch from regimens containing EFV to STR based on

Table 9 - *Summary of rationale/advantages/disadvantages of other optimization strategies.*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*Literature*
From ABC to TDF (a)	Prevent drug specific toxicity	Long term virological response; improves lipid profile	Higher number of adverse events and therapy interruption; increased creatinine levels; no information available about the status of bone tissue	[BI]	(Behrens *et al.* 2012; Campo *et al.*2013; Moyle *et al*. 2015)
From TDF to ABC (b)	Prevent drug specific toxicity	Lower impact on bone turnover	No information available about impact on kidney, cardiovascular system and lipid profile; cardiovascular toxicity consequent ABC administration cannot be ruled out.	[BII]	(Harris *et al.* 2013; Llibre *et al.* 2013; Negredo *et al.* 2015; Negredo *et al.* 2014)
From EFV to NVP (c)	Prevent drug specific toxicity	Improved lipid profile; higher CNS penetration; reduced neurological toxicity	Short term skin and liver toxicity; not available in co-formulation	[BI]	(Parienti *et al.* 2007; Pedrol *et al.* 2015; Winston *et al.* 2004)
From ATV/r to ATV (d)	Prevent drug specific toxicity	Reduction of hyperbilirubinemia; slight normalization of lipid level; lower incidence of adverse effects	Lower genetic barriers; contraindicated in combination with TDF and antacids	[CI]	(Ghosn *et al.* 2010; Squires *et al.* 2012; Wohl *et al.* 2016)
From EFV/FTC/TDF to EVG/COBI/FTC/ TAF FDC (e)	Prevent toxicity	Higher virological success rates; lower incidence of adverse effects; reduced proteinuria and improvement of BMD	Slight impairment of lipid profile (long term clinical consequences need to be assessed)	[AI]	(Mills *et al.* 2015c)
Da EVG/COBI/FTC/ TDF FDC a EVG/ COBI/FTC/TAF FDC (f)	Prevent toxicity	Lower incidence of adverse effects; reduced proteinuria and improvement of BMD	Slight impairment of lipid profile (long term clinical consequences need to be assessed)	[AI]	(Mills *et al.* 2015c)

(a) Treatment simplification from ABC to TDF led to similar virological response in two RCTs, however patients in the ABC arm showed a significant improvement of lipid profiles, while, in one of the studies, patients in TDF arm showed a significant decrease of glomerular filtration rate. Conversely, in the SWIFT study, a lower number of virological failures was recorded in the TDF arm; lipid profile improvement and decreased cardiovascular risk together with kidney function impairment were reported in both study arms, although kidney function was more severely affected in patients treated with TDF.
(b)A retrospective analysis performed on 225 patients who underwent therapy simplification from TDF to ABC showed the maintenance of the virological response together with an improvement of kidney functionality in patients treated with either ATV or other antiretroviral drugs. In three studies performed in Spain, following simplification to ABC, decrease of bone turnover rate and improvement, although not significant, of femoral bone density were observed.
(c) A small randomized clinical study (SIROCCO) performed in France showed the improvement of lipid profile together with a reduction of adverse events targeting SNC in patients switching from EFV to NVP, while reporting similar virological response compared to the control arm. Results from a pharmacokinetic study enrolling 15 patients suggest that simplification from EFV to NVP can be started at the dose of 200 mg twice a day in the first two weeks to reach therapeutic concentration more rapidly. Simplification to NVP from regimens associated with adverse events targeting CNS (in particular EFV) in a cohort of 129 virologically suppressed patients led to increase therapy adherence and improved patients' life quality.
(d) Recommended in patients who do not tolerate RTV. Not recommended for co-administration with TDF or antacids. In this case, if therapy interruption is required due to toxicity, plasma ATV concentration should be monitored regularly using TDM.
(e) The GS-109 study demonstrated superior virological success at week 48, improvement of bone mineralization and kidney as well as tubular functionality together with a slight impairment of the lipid profile (whose long term clinical implications need to be assessed) in 376 patients.
(f) The GS-109 study demonstrated non-inferiority in terms of virological success at week 48, improvement of bone mineralization and kidney and tubular functionality together with a slight impairment of the lipid profile (whose long term clinical implications need to be assessed) in 459 patients.

Table 10 - *Indications for treating HIV/HCV coinfection.*

Rate of recommendation/Level of evidence	*Clinical conditions*
Maximum [AI]	Patients with unbalanced liver disease or hepatocellular carcinoma who are eligible for liver transplant.
	Patients who underwent solid organ transplantation (liver or other organs).
	Patients with hepatic cirrhosis or advanced fibrosis (histology: >F2 METAVIR or S3 ISHAK and/or Stiffness >10 as determined by fibroscan and/or FIB4 >3.25)§.
	Patients with cryoglobulinemia and symptomatic vasculitis.
	Patients with nephrotic syndrome or membranoproliferative glomerulonephritis non HIV associated.
Very high [AII]	All remaining conditions in patients co-infected with HIV/HCV (Berenguer et al. 2014; Macias et al. 2015).

§There are no evidences of increased survival after HCV eradication in patients suffering from unbalanced cirrhosis or hepatocellular carcinoma . The choice of whether or not to treat a patients must be evaluated for each case separately and the therapy must be managed together with liver failure specialists.

Table 11 - *HCV therapy guidelines for HIV/HCV co-infected patients.*

Therapeutic options for HCV therapy				
Genotype	**Therapeutic regimen**	**Duration of treatment and RBV use**		
		Not-cirrhotic	**Compensated cirrhosis**	**Decompensated cirrhosis**
1 e 4	SOF + SMP ± RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV (a)	Not recommended
	SOF/LDV ± RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotic patients or before/after transplant (a)	
	SOF + DCV ± RBV	12 weeks without RBV	12 weeks with RBV or 24 weeks without RBV in cirrhotic patients or before/after transplant (a)	
	OBV/PTV/r + DSV ± RBV	12 weeks without RBV for patients infected with HCV genotype 1[b] 12 weeks with RBV for patients infected with HCV genotype 1[a]	12 weeks without RBV for patients infected with HCV genotype 1b 24 weeks with RBV for patients infected with HCV genotype 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in patients infected with HCV genotype 4	24 weeks in patients infected with HCV genotype 4	Not recommended
	GRZ + ELB ± RBV	12 weeks without RBV (c)	12 weeks without RBV for naïve patients infected with HCV genotypes 1a, 1b, and 4 16 weeks with RBV for experienced patients infected with genotype 1 and 4 (c)	Not recommended (c)
	SOF + VEL ± RBV	12 weeks without RBV(c)		12 weeks with RBV(c)
2	SOF + DCV ± RBV	12 weeks without RBV	12 weeks without RBV o 12 weeks with RBV	
3	SOF + PEG-IFN/RBV	12 weeks in patients who are eligible for PEG-IFN therapy	12 weeks in patients who are eligible for PEG-IFN therapy	Not recommended
	SOF + DCV ± RBV(iii)	12 weeks without RBV	16-24 weeks with RBV	
5 and 6	SOF + VEL ± RBV	12 weeks without RBV (c)		12 weeks with RBV (c)

(a) patients with cirrhosis and predictors of negative response to therapy can be treated with 24 weeks with RBV (predictors of negative response: previous failure with interferon-based therapy, platelet count <75x10^3/µl).
(b) Possible extension to 16 weeks in cirrhotic patients naive to treatment and in relapsing patients after PEG-IFN/RBV; up to 20 weeks in cirrhotic patients with previous history of failure with PEG-IFN based therapies.
(c) Based on expert opinion and preliminary data from registration studies and/or expanded access programs. For more information we refer to the on line version of the *EACS Guidelines ver 8.01 October 2015*.

Table 12 - *Indications for treatment of patients showing no sustained virological response to therapeutic regimens including direct acting drugs(European AIDS Clinical Society 2015).*

The presence as well as the development of mutations associated to resistance should be assessed by sequencing one or more samples obtained after completion of therapy and, where available, also on samples obtained before and during treatment [CIII].
In therapeutic failures following treatment with therapeutic regimens including protease inhibitors (Telaprevir, Boceprevir, Simeprevir) with or without Sofosbuvir:
Sofosbuvir + NS5A inhibitor (Ledipasvir for HCV genotype 1 and 4 or Daclatasvir for all genotypes) + Ribavirin for 24 weeks in cirrhotic patients or 12 weeks in non-cirrhotic patients; presence of viral variants associated to reduced efficacy of NS5A inhibitors should be taken in consideration to evaluate therapy efficacy [CIII];
When available, the combination of Grazoprevir + Elbasvir without RBV for 12-16 weeks should be also considered as therapeutic option [CIII].
In therapeutic failures including only Sofosbuvir as direct acting antiviral and in therapeutic failures including NS5A inhibitors (Ledipasvir, Daclatasvir, and Ombitasvir) in combination with Sofosbuvir:
The following parameters should be evaluated in a specialized centre:
Benefits of immediate retreatment compared to deferring treatment in favor of watchful waiting [CIII];
Clinical and virological features [CIII];
Previous exposure to HCV protease inhibitors (Paritaprevir/r, Simeprevir, Boceprevir, or Telaprevir) [CIII].
Treat with:
Sofosbuvir, RBV and PEG-IFN in cases with a favorable cost/benefit ratio, particularly in infections sustained by genotypes 2 or 3 [CIII];
Sofosbuvir, RBV and protease inhibitors in presence or absence of non nucleoside polymerase inhibitors. Moreover, treatment can be prescribed in selected cases harboring HCV genotype 1 or 4 in which therapy could not be delayed to wait for more information about efficacy of second generation drugs (Velpatasvir, Elbasvir, Grazoprevir) [CIII].
Determination of virological response via HCV- RNA quantification should be performed more frequently during the course of treatment [CIII].

INSTI [AI], the switch from regimens containing EFV to STR based on TDF/FTC/RPV has been evaluated only in observational studies which nevertheless showed no risk of virological failure or toxicity [BII].

Other optimization strategies: We refer the reader to Table 9.

THE USE OF NEW ANTI HCV DRUGS FOR THE THERAPEUTIC MANAGEMENT OF HIV/HCV INFECTED PATIENTS

Treatment with direct acting antivirals (DAAs) alone or in combination with Pegylated Interferon should be considered for all HIV infected patients with chronic hepatitis virus infections. In case of similar efficacy, interferon free therapies should be preferred.

The following reasons support the eradication of HCV infection in all HIV/HCV co-infected patients:

- Progression of liver disease results in higher mortality rates due to hepatocarcinoma and unbalanced cirrhosis.
- Proven negative impact of HCV infection:
  - Reduced kidney functionality and increased mortality unrelated to liver disease,
  - Impaired CD4 T cell recovery during c-ART.
- Possible negative impact of HCV infection on:
  - HIV progression even in presence of c-ART,
  - Osteoporosis,
  - Cardiovascular diseases,
  - Onset of diabetes.

HCV eradication is associated with a lower likelihood of unbalanced liver disease and with reduced mortality rates in patients with advanced liver disease, as well as in patients with moderated fibrosis (Berenguer *et al.,* 2012; Berenguer *et al.,* 2014; Macias *et al.,* 2015). We refer the reader to *Tables 10, 11* and *12* for recommendations for HCV treatment prioritization, including drug regimens and special conditions.

List of abbreviations

3TC: lamividuine; ABC: abacavir; ATV/r: ritonavir boosted atazanavir; ARV: antiretroviral drugs; BMD: bone mineral density; cART: combined antiretroviral therapy; COBI: cobicistat; CSF: cerebrospinal fluid; DCV: Daclatasvir; DTG: dolutegravir; DRV/r: ritonavir boosted darunavir; EFV: efavirenz; ELB: elbasvir; EVG: elvitegravir; FDC: fixed dose combinations; FTC: emitricitabine; GFR: glomerular filtration rate; GRZ: grazoprevir; LDV: Ledipasvir; LDR: Less Drug Regimen; LPV/r: ritonavir boosted lopinavir; NRTI: nucleoside reverse transcriptase inhibitor; HSR: hypersensitivity reactions; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NVP: nevirapine; OBV: ombitasvir; PEG-IFN: pegylated Interferon; PI/r: ritonavir boosted protease inhibitor; PTV: paritaprevir; RBV: ribavirine; RAL: raltegravir; RCT: randomized clinical trials; RPV: rilpivirine; RTV: ritonavir; SMP: simeprevi.; SOF: sofosbuvir; STR: single tablet regimens; SVR: sustained virological response; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; VEL: velpatasvir.

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