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Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update December 2014

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INTRODUCTION

This short version complies with the intention expressed in the introduction to the full text Italian Guidelines for the use of antiretroviral drugs and the diagnostic-clinical management of people with HIV-1 infection. By definition, this version should not be considered completely exhaustive with respect to the full text version of the Guidelines (HIV/AIDS Italian Expert Panel, 2014).

This publication highlights only the main updates of the 2014 Guidelines version in respect to the 2012 edition (Antinori, et al. 2012), that is: when and what to start combined antiretroviral therapy (cART), treatment optimization, retention in care, the use of new anti HCV drugs for the therapeutical management of HIV/HCV infected patients. Recommendations in these guidelines are based upon scientific evidence and expert opinion (Table 1).

It was decided to give not to discuss in toto certain fundamental parts of the extended versions such as comorbidities management, the populations requiring special attention (elderly, women, immigrants, children), the conditions requiring special attention (drug and/or alcohol addiction, detention) or the situations requiring special attention (transplants). For all these populations, conditions or situations, it should be referred at the full text version of the Guidelines (HIV/AIDS Italian Expert Panel, 2014 #604).

Lastly, it was decided to refer the reader to the extended version for all bibliographic citations, except for the references cited at the end of this version concerning the 2014 updates.

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

a) Degree of recommendation	
A	Highly recommended
B	Moderately recommended
C	Optional
b) 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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WHEN TO START

Antiretroviral therapy is recommended in all the subjects with chronic HIV infection who are willing to start therapy, regardless of their CD4 T cell count or viral load.
In particular, considering the evidences and the strength of the clinical studies:

- cART is strongly recommended in all the individuals with a CD4 T cell count below 500 cells/µl. Rating of recommendation is [AII] in patients with CD4 T cells count between 350 and 500 cells/µl and [AI] for the individuals with a CD4 T cell count lower than 350 cells/µl.
- cART is moderately recommended [BIII] in patients with a CD4 T cell count above 500 cells/µl. The rate of recommendation for these subjects can switch to [AII], highly recommended, if a decrease in CD4 T cell count of more than 100 cells/µl/year is observed or if the levels of plasma HIV RNA are higher than 20.000 copies/ml.

Adequate counselling should be given to patients starting cART with a high CD4 T cell count (>500 cells/µl). Patients need to be aware of the potential benefits of early therapy start (decrease of viral replication and chronic inflammation, better immunological recovery, reduced risk of AIDS related and not AIDS related morbidity, reduced risk of transmission) as well as of the risks associated with long term therapy (potential drug toxicities, risks related to incomplete adherence).
Healthcare workers should highlight the importance of a complete adherence to cART, particularly in patients with a CD4 T cell count within the standard range for healthy population who start therapy in an early phase of infection.
Moreover, antiretroviral treatment is recommended in the following groups of patients in order to prevent HIV transmission:

- Patients who have HIV negative sexual partners, regardless of their CD4 T cell count or viral load [AI].
- HIV positive individuals requesting treatment, regardless of the reason [AIII].

If offered to the patients, treatment as prevention must be discussed in a dedicated meeting where the health care specialist will provide extensive information and discuss therapeutic options with the patient. Since the effectiveness of treatment as prevention strongly relies on the willingness and ability of patients to adhere to antiretroviral treatment, the patient's decision of starting therapy must be taken in absence of any psychological pressure and only after an adequate counselling. Providing sufficient information to understand all the advantages and disadvantage of early antiretroviral therapy start as well as the necessary time frame to process the information and take a considered decision must be intended as a standard of care to be pursued in all HIV infected patients, regardless of their CD4 T cell counts [AIII].
Finally, antiretroviral therapy is recommended in patients with primary HIV infection (PHI). This group of patients includes individuals presenting symptoms consistent with an acute retroviral syndrome (acute patients) and individuals diagnosed within 6 months from the possible transmission events (recent infections). Providing antiretroviral treatment during PHI represents a unique intervention opportunity

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

Clinical condition	*CD4 T lymphocyte count*	*Recommendation for treatment*	*Strength evidence*	*Related literature*
Asymptomatic patients with acute or recent infection	Any value	Moderately recommended	[BII]	(Schacker *et al*. 1996; Kahn and Walker 1998; Oxenius *et al*. 2000; Rosenberg *et al*. 2000; Fidler *et al*. 2002; Pilcher *et al*. 2004; Mehandru *et al*. 2006; Brenner *et al*. 2007; Daar *et al*. 2008; Lockman and Creek 2009; Ananworanich *et al*. 2012; Grijsen *et al*. 2012; Le *et al*. 2013; Saez-Cirion *et al*. 2013)
Symptomatic patient with acute or recent infection	Any value	Highly recommended	[AII]	

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

Clinical condition	*CD4 T lymphocyte count*	*Recommendation for treatment*	*Strength evidence*	*Related literature*
Asymptomatic	<350 cells/µl	Highly recommended	[AI]	(Badri *et al*. 2004; Moh *et al*. 2007; Wong *et al*. 2007; Strategies for Management of Antiretroviral Therapy Study *et al*. 2008; When To Start *et al*. 2009; Severe *et al*. 2010)
	350-500 cells/µl	Highly recommended	[AI]	(Cozzi Lepri *et al*. 2001; Mocroft *et al*. 2007; Strategies for Management of Antiretroviral Therapy Study *et al*. 2008; When To Start *et al*. 2009; Collaboration *et al*. 2010; Severe *et al*. 2010; Cohen *et al*. 2011b; Collaboration *et al*. 2011; Plettenberg *et al*. 2011; Collaboration of Observational *et al*. 2012; Hogan *et al*. 2012; Lucero *et al*. 2013; Grinsztejn *et al*. 2014)
	500 cells/µl	Moderately recommended Particularly recommended if one or both the following conditions are observed: - CD4 T cell decrease >100 cells/µl/year; - HIV-RNA >20.000 copies/ml	[BIII] [AII] [AII]	(Hogan *et al*. 2012; Lucero *et al*. 2013; Grinsztejn *et al*. 2014; Montaner *et al*. 2014; Nolan and Wood 2014) [30-34]
AIDS	Any value	Highly recommended	[AI]	(Badri *et al*. 2004; Moh *et al*. 2007; Wong *et al*. 2007; Strategies for Management of Antiretroviral Therapy Study *et al*. 2008; When To Start *et al*. 2009; Severe *et al*. 2010)
Pregnancy	Any value	Highly recommended	[AI]	(Hoffman *et al*. 2010; Tubiana *et al*. 2010)
HIV-associated nephropathy (HIVAN)	Any value	Highly recommended	[AII]	(Schwartz *et al*. 2005; Estrella *et al*. 2006; Lichtenstein *et al*. 2008)
Non-AIDS defining cancers	Any value	Highly recommended	[AII]	
HIV-associated Neurocognitive Disorders (HAND)	Any value	Highly recommended for HIV-Associated Dementia (HAD) or Mild Neurocognitive Disorder (MND)	[AII]	(Mellgren *et al*. 2005; Robertson *et al*. 2007; Cysique *et al*. 2009)
Chronic HBV infection requiring treatment	Any value	Highly recommended. In cases in which there is indication for HBV treatment nucleoside analogues are recommended.	[AII]	(Thio *et al*. 2002, Peters *et al*. 2006; Matthews *et al*. 2008)
Treatment as prevention: serodiscordant couples and other conditions	Any value	Always in case of highly motivated patients	- Serodiscordant couples: [AI] - Multiple unprotected sexual intercourse; presence of other sexually transmitted diseases [AII]	(Attia *et al*. 2009; Donnell *et al*. 2010; Reynolds *et al*. 2011)

during the clinical course of the disease (Mehandru *et al.* 2006) and it is of particular relevance for the spreading of the disease since subjects during PHI have the highest likelihood to transmit the infection. The rate of recommendation for treatment of acute and recent infections depends on the presence [AII] or absence [BII] of symptoms.
Recommendations (including rates of recommendation, levels of evidence and relevant literature) concerning the opportunity to treat in different clinical conditions in patients with acute or chronic infection 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 2014)].

THERAPEUTIC REGIMENS

The goal of starting cART in HIV positive patients is the reduction of HIV related mortality and morbidity and the consequent improvement of patient's quality of life. Achievement of a complete virological suppression (decrease of plasma HIV RNA levels below the limit of detection of standard diagnostic tests) within 3-6 months from the start of cART is necessary to reach this goal.
Moreover, suppression of viral replication is also associated to immunological recovery and reduction of the inflammatory state and of its associated complications. Because of their relevance to public health, also the indirect effects potentially associated with suppression of viral replication such as a reduced risk of HIV transmission and the resulting contraction of HIV epidemics as well as the positive effects in term of HIV de-stigmatization must be actively pursued.
The recommended pharmacological treatment for HIV patients naïve to therapy is usually made of a combination of different antiretroviral drugs, called therapeutic regimen. In this regard, 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.
The critical factor determining the efficacy of a pharmacological treatment lies in its capacity to meet patient's clinical and non-clinical needs. Table 4 provides a list of the factors that play a role in determining the efficacy of a therapy and therefore need to be considered in order to identify the best first regimen for a given patient.
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 chapter 3, Treatment Optimization).

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 (HIV/AIDS Italian Expert Panel, 2014).

In agreement with the recommendations for the treatment of acute and recent infections, pharmacological treatment of HIV patients at these stages of infection needs to include one of the regimens recommended for subject with high viral load (HIV RNA >100,000 copies/ml) [AII]. Despite the lack of evidences deriving from clinical trials, in patients characterized by extremely high 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. Moreover, clinicians might consider the use of a combination of four drugs instead of three, selecting the molecules that guarantee the fastest virological suppression [CIII].

Classification and degree of recommendation of cART regimens.

Recommended regimes (Table 5a*)* [A] - Regimens meeting all the following criteria:

- Proven efficacy in controlled, randomized clinical trials with sufficient potency (quality of the study, size and characteristics of the control group);

TABLE 5A - *Antiretroviral regimens recommended for starting cART.*

Regimen	*Degree of recommendation/ Level of evidence*	*Related literature*
TDF/FTC+EFV	[AI]	(DeJesus *et al.* 2004; van Leth *et al.* 2004; Gallant *et al.* 2006; Arribas *et al.* 2008; Riddler *et al.* 2008; Lennox *et al.* 2009; Sax *et al.* 2009; Post *et al.* 2010; Daar *et al.* 2011; Molina *et al.* 2011; Sax *et al.* 2011; Sax *et al.* 2012; Cohen *et al.* 2013b; Rockstroh *et al.* 2013; Walmsley *et al.* 2013; Carey 2014; Cohen *et al.* 2014; Wohl *et al.* 2014)
ABC/3TC+EFV (recommended if HIV-RNA <100000 copies/ml)	[AI]	(Sax *et al.* 2009; Post *et al.* 2010; Daar *et al.* 2011; Sax *et al.* 2011)
TDF/FTC/RPV (useable only if HIV-RNA <100000 copies/ml)	[AI]	(Molina *et al.* 2011; Cohen *et al.* 2012; Cohen *et al.* 2013a)
TDF/FTC+ATV/r	[AI]	(Ortiz *et al.* 2008; Lennox *et al.* 2009; Molina *et al.* 2010; Daar *et al.* 2011; Eron *et al.* 2011; Soriano *et al.* 2011; Sax *et al.* 2012; Orkin *et al.* 2013; Rockstroh *et al.* 2013; Clumeck *et al.* 2014; Landovitz *et al.* 2014)
ABC/3TC+ATV/r (recommended only if HIV-RNA <100000 copies/ml)	[AI]	(Sax *et al.* 2009; Daar *et al.* 2011; Sax *et al.* 2011)
TDF/FTC+DRV/r	[AI]	(Ortiz *et al.* 2008; Orkin *et al.* 2013; Clotet *et al.* 2014; Landovitz *et al.* 2014)
ABC/3TC+DRV/r	[AII]	(Clotet *et al.* 2014)
TDF/FTC+RAL	[AI]	(Lennox *et al.* 2009; Raffi *et al.* 2013a; Raffi *et al.* 2013b; Rockstroh *et al.* 2013; Landovitz *et al.* 2014)
ABC/3TC+RAL	[AII]	(Raffi *et al.* 2013a; Raffi *et al.* 2013b)
TDF/FTC/EVG/COBI	[AI]	(DeJesus *et al.* 2012; Sax *et al.* 2012; Clumeck *et al.* 2014; Wohl *et al.* 2014)
TDF/FTC+DTG	[AI]	(Raffi *et al.* 2013a; Raffi *et al.* 2013b; Clotet *et al.* 2014)
ABC/3TC+DTG	[AI]	(Raffi *et al.* 2013a; Raffi *et al.* 2013b; Walmsley *et al.* 2013; Clotet *et al.* 2014)

NNRTI based regimens are not recommended in presence of mutations conferring resistance to NRTI and NNRTI.
Due to the occurrence of hypersensitivity reactions (HSR), ABC is not recommended in subjects harbouring the HLA allele B*5701.
The approved dosage of DRV/r is 600/100 mg once a day.
EVG/COBI is contraindicated in patients with impaired renal function (GFR ml/min/1.73m^2). Information on kidney toxicity of this combination is limited. The standard dosage of EFV is 600 mg/once a day. The *off label* dosage of 400mg twice daily proved to be not inferior to standard dosage if prescribed in association with TDF/FTC.
"/" = co-formulated; "+" = not co-formulated.

- Favourable acceptability, tolerability, and safety profiles;
- Well established use in clinical practice based on the number and extent of clinical studies, on the data deriving from observational studies, or on the extensive clinical use after the launch on the market.

Alternative regimens (Table 5b) [B] - Partially meeting the criteria for recommendation because of the following reasons:

- Regimen efficacy is supported by incomplete evidences;
- Suboptimal acceptability, tolerability, and safety profiles;
- Supported only by a limited amount of clinical data and lacking extensive clinical use in real life.

Alternative regimens are suggested in cases where the patient does not tolerate or is unable to take recommended drugs (due to resistance, toxicity or intolerance).

Optional regimens (Table 5b) [C] - Regimens showing:

- Insufficient or evidences supporting regimen efficacy;
- Suboptimal acceptability, tolerability, and safety profiles.

Optional regimens are suggested in cases where

TABLE 5B - *Alternative and optional drugs combinations for first regimens.*

	Regimen	*Degree of recommendation/Level of evidence*	*Related literature*
Alternative	TDF/FTC+LPV/r	[BI]	(Ortiz *et al*. 2008; Riddler *et al*. 2008; Smith *et al*. 2009; Molina *et al*. 2010; Orkin *et al*. 2013)
	ABC/3TC+LPV/r	[BI]	(Smith *et al*. 2009)
	TDF/FTC+NVP	[BI]	(van Leth *et al*. 2004; Soriano *et al*. 2011; Cain *et al*. 2012)
	DRV/r + RAL (only 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)
	LPV/r + 3TC	[BI]	(Cahn *et al*. 2014)
	TDF/FTC+ATV/COBI	[BI]	(European Medicines Agency 2013; Gallant *et al*. 2013)
	ABC/3TC+ATV/COBI	[BIII]	(Gallant *et al*. 2013)
	TDF/FTC+DRV/COBI	[BIII]	(Gallant *et al*. 2013)
	ABC/3TC+DRV/COBI	[BIII]	(Gallant *et al*. 2013)
Optional	TDF+3TC+EFV	[CI]	(Gallant *et al*. 2004)
	ABC/3TC+RPV (only if HIV-RNA <100.000 copies/ml)	[CII]	(Cohen *et al*. 2011a; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b)
	LPV/r + RAL	[CI]	(Reynes *et al*. 2013)
	LPV/r + MVC	[CI]	(Nozza *et al*. 2014)

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.
The approved dosage of DRV/r is 600/100 mg once daily.
EVG/COBI is contraindicated in patients with impaired renal function (GFR ml/min/1.73 m^2). Information on kidney toxicity of this combination is limited.
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 its usual dose (400 mg/day) in the first 14 days of treatment using extended-release tablets.
"/" = co-formulated; "+" = not co-formulated;

the patient does not tolerate or is unable to take recommended or alternative regimens (due to resistance, toxicity or intolerance).
Table 6 reports the degree of recommendation and level of evidence as well as pro and cons of single drugs and drug combinations taking in account information concerning tolerability and toxicity, pharmacological interactions, formulations, posology and costs deriving from randomized clinical trials.

TREATMENT OPTIMIZATION

Therapy simplification: This treatment scheme, also known as Less Drug Regimen (LDR), refers to an induction-maintenance strategy and is intended to reduce the number of antiretroviral drugs included in a given regimen. Once plasma viral load is not detectable anymore and immunoreconstituition is taking place (at least 6 months after achieving viral suppression), the aim of switching to a LDR is to maintain viral control while at the same time limiting or avoiding long term toxicities, increasing tolerability and reducing pharmacological interactions. Such approach is of particular interest in light of the increasing rates of comorbidities and of the more widespread use of non-antiretroviral medications related to the aging of the HIV population.
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 7). Initially, dual therapy regimens were developed with the aim of excluding nucleoside reverse transcriptase inhibitors (NRTIs) from the therapeutic combinations, since these drugs show higher long-term toxicities. Recently, combinations including a ritonavir boosted protease inhibitors (PI/r) in combination with lamivudine (3TC) and/or emitricitabine (FTC) have been evaluated, given that the toxicities associated with the use of these NRTIs are significantly lower or absent

TABLE 6 - *Summary of rationale/advantages/disadvantages of first line regimens.*

ARVs class	*Drug(s)*	*Evidences of efficacy deriving from RCT*	*Advantages*	*Disadvantages*
N(t)RTI (2 drugs backbone)	ABC/ 3TC	- Evaluated in comparison studies against TDF/FTC in association with EFV, ATV/r, DTG. - Inferior to TDF/FTC if used in association with ATV/r e EFV in patients with basal HIV RNA viral load ≥100,000 copies/ml (Sax *et al*. 2009; Post et al. 2010; Sax *et al*. 2011). - Comparable efficacy to TDF/FTC, if used in association to RAL e DRV/r demonstrated only in subgroup analysis of RCT (Raffi *et al*. 2013a; Raffi *et al*. 2013b; Clotet *et al*. 2014). - Limited information concerning its association with RPV (Cohen *et al*. 2012). - Superior to TDF/FTC (in association with EFV) if used in association with DTG (Walmsley et al. 2013).	- Once a day regimen - Available in co-formulation with DTG. - No food-drug interactions reported. - No evidences of nephrotoxicities (Post et al. 2010; Daar *et al*. 2011). - Generic, not-co-formulated, forms of ABC e 3TC are available (higher pill burden/day).	- Due to the high risk of developing HSR, ABC is not recommended in subjects harbouring the HLA allele B*5701. - The use of ABC has been associated with an increased risk of cardiovascular disease in observational studies. RCT and meta-analysis did not confirm these observations (Group *et al*. 2008; Ding *et al*. 2012).
	TDF/ FTC	- Used as standard NRTI backbone with all recommended regimens. - Only one recommended NRTI backbone in association with RPV and EVG/COBI. - Superior to ABC/3TC in association with EFV and ATV/r in patients with baseline HIV viremia >100,000 copies/ml(Sax *et al*. 2009; Post *et al*. 2010; Sax *et al*. 2011).	- Once a day regimen - Available in co-formulation and single tablet formulation with EFV, RPV, EVG/COBI. - No food-drug interactions reported. - Activity against HBV. Preferred over 3TC alone in HBV/HIV co-infected patients.	- Use of TDF/FTC has been associated with an higher risk of kidney failure and renal tubular dysfunction (Scherzer *et al*. 2012; Gupta *et al*. 2014; Jose *et al*. 2014). Association with PI/r and COBI could further increase these risks (DeJesus *et al*. 2012; Young *et al*. 2012; Ryom *et al*. 2013; Baxi *et al*. 2014; Clumeck *et al*. 2014; Mwafongo *et al*. 2014). - Higher risk of bone mineral density (BMD) reduction compared to ABC/3TC (McComsey *et al*. 2010; Stellbrink *et al*. 2010).

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ARVs class	*Drug(s)*	*Evidences of efficacy deriving from RCT*	*Advantages*	*Disadvantages*
NNRTI	EFV	- Evaluated in association with both TDF/FTC and ABC/3TC. - Evaluated in comparison studies against all other therapy combinations, except DRV/r. - Not-inferior to RPV, ATV/r, and EVG/COBI (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b). - Superior to RPV (non STR) in patients with baseline HIV viremia >100,000 copies/ml (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b). - Inferior to RAL in long term observation (Not inferior at the primary endpoint at 48 weeks) (Lennox *et al*. 2009; Rockstroh *et al*. 2013). - Inferior to DTG (at 48 weeks) (Walmsley *et al*. 2013).	- Once a day regimen. - Available in co-formulation with TDF/FTC. - Extensive clinical use. - Available as generic drug.	- Increased risk of resistance mutations at failure compared to PI/r and DTG (Riddler *et al*. 2008; Daar *et al*. 2011; Walmsley *et al*. 2013). Not recommended in patients harbouring transmitted resistance to NNRTIs. - Use of EFV in the first six weeks of pregnancy has been associated to an higher risk of foetal malformations (neural tube defects); however in recent studies and meta-analysis the estimated risk of developing foetal malformations was not superior to other ARVs (Ford *et al*. 2014; Sibiude *et al*. 2014). - Neurological and psychiatric effects (dizziness and trouble sleeping) mostly during the first months of treatment, with possible long term persistence (Mills *et al*. 2013a). - Use of EFV is associated to depression (not confirmed in all the studies), and higher risk of suicidal tendencies in RCT re-analysis (not confirmed by pharmacovigilance data) (Mollan *et al*. 2014; Napoli *et al*. 2015). - Use of EFV is associated with a higher risk of developing dyslipidemia compared to RPV and integrase inhibitors (INI) (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b) (Lennox *et al*. 2009; Cohen *et al*. 2013b; Rockstroh *et al*. 2013; Walmsley *et al*. 2013; Cohen *et al*. 2014). - Use of EFV is associated with a higher risk of developing cutaneous rash compared other anchor drugs (Riddler *et al*. 2008; Lennox *et al*. 2009; Cohen *et al*. 2011a; Daar *et al*. 2011; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013a; Cohen *et al*. 2013c; Nelson *et al*. 2013; Rockstroh *et al*. 2013; Walmsley *et al*. 2013; Cohen *et al*. 2014; Molina *et al*. 2014a) - Possible pharmacological interactions (EFV is a substrate and an inducer of CYP3A4). - EFV should be taken at empty stomach, preferably at bedtime (meals significantly enhance EFV absorption and thus increase drug-related toxicities).
	RPV	- Evaluated mostly in association with TDF/FTC. Limited data available for the association with ABC/3TC. - Evaluated in comparative studies against EFV. - Not inferior to EFV if total, not stratified, population is considered; inferior to EFV in patients with baseline viremia >100,000 copies/ml, with higher risk of developing resistance (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b). - Not inferior to EFV in STR with TDF/FTC in patients with baseline viral load >100,000 copies/ml; superior efficacy in patients with baseline viral load <100,000 copies/ml (Cohen *et al*. 2013b; Cohen *et al*. 2014). - Approved for use in patients naive to antiretroviral therapy only if baseline viremia is lower than 100,000 copies/ml. Not recommended if CD4 T cell count is lower than 200 cells/µl due to the higher risk of virological failure and resistance.	- Once a day regimen. - Available in co-formulation with TDF/FTC. - Good tolerability profile compared to the majority of other anchor drugs. - Minor neuropsychiatric effects (dizziness, trouble sleeping), cutaneous rash, and dyslipidemia compared to EFV (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b) (Cohen *et al*. 2013b; Cohen *et al*. 2014) (Mills *et al*. 2013a).	- Increased risk of resistance mutations at failure compared to EFV (Cohen *et al*. 2011a; Molina *et al*. 2011; Cohen *et al*. 2012; Cohen *et al*. 2013c; Nelson *et al*. 2013; Molina *et al*. 2014b). Not recommended in patients harbouring transmitted resistance to NNRTIs. - Possible pharmacological interactions (RPV is a substrate and an inducer of CYP3A4). - Recommended administration with food. - Co-administration of RPV with proton pump inhibitors is contraindicated - Caution should be used when RPV is co-administered with H2 antagonists or drugs with known risk of torsade de pointes-type- arrhythmia.

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ARVs class	*Drug(s)*	*Evidences of efficacy deriving from RCT*	*Advantages*	*Disadvantages*
PI/r	ATV/r	- Evaluated in association with either TDF/FTC or ABC/3TC. - Evaluated in comparison studies against all other anchor drugs, except for RPV and DTG. - Not inferior to EFV and EVG/COBI (Daar *et al*. 2011; DeJesus *et al*. 2012; Clumeck *et al*. 2014). - Equivalent to DRV/r and RAL (Landovitz *et al*. 2014).	- Once a day regimen. - Lower risk of resistance mutations at failure compared to NNRTI, EVG/COBI, and RAL (Sax *et al*. 2009; Daar *et al*. 2011; DeJesus *et al*. 2012; Clumeck *et al*. 2014; Landovitz *et al*. 2014). - Extensive clinical use	- Co-formulations with other ARVs are not available. - Risk of developing hyperbilirubinaemia and yellow jaundice. - Risk of developing gastro-intestinal adverse effects. - Higher risk of discontinuation due to adverse events (indirect hyperbilirubinaemia; gastrointestinal adverse effects) compared to DRV/r and RAL (Landovitz *et al*. 2014). - Increased risk of kidney and gallbladder lithiasis. - Increased risk of kidney failure and proximal renal tubulopathy (if used in association with TDF) (DeJesus *et al*. 2012; Clumeck *et al*. 2014) (Young *et al*. 2012; Ryom *et al*. 2013). - Higher risk of developing dyslipidemia compared to RAL and EVG/COBI (DeJesus *et al*. 2012; Clumeck *et al*. 2014; Landovitz *et al*. 2014). - Higher risk of BMD reduction compared to RAL (if used in association with TDF) (Brown *et al*. 2014). - Co-administration with proton pump inhibitors can reduce absorption of ATV. - Possible pharmacological interactions (ATV is a substrate and an inducer of CYP3A4). - Recommended administration with food.
	DRV/r	- Evaluated in association with TDF/FTC. Association with ABC/3TC has been evaluate in only one RCT. - Evaluated in comparison studies against ATV/r, RAL, and DTG. Comparative studies against NNRTIs are missing. - Equivalent to ATV/r and RAL (Landovitz *et al*. 2014). - Inferior to DTG (at primary endpoint at 48 weeks) (Clotet *et al*. 2014).	- Once a day regimen. - Lower risk of resistance mutations at failure compared to NNRTI e INI (non DTG) (Ortiz *et al*. 2008; Orkin *et al*. 2013; Landovitz *et al*. 2014). - Lower risk of discontinuation due to adverse events (indirect hyperbilirubinaemia; gastrointestinal adverse effects) compared to ATV/r (Landovitz *et al*. 2014). - Extensive clinical use.	- Co-formulations with other ARVs are not available - Higher risk of developing cutaneous rash compared to other drugs of the same class (Ortiz *et al*. 2008; Orkin *et al*. 2013). - Risk of developing gastro-intestinal adverse effects. - Higher risk of developing dyslipidmia and BMD reduction compared to RAL (if used in association with TDF). - Possible pharmacological interactions (DRV/r is a substrate and an inducer of CYP3A4). - Administration with food is recommended.
INI	RAL	- Evaluated in comparative studies against all other recommended anchor drugs except RPV and EVG/COBI. - Superior to EFV in long term studies (not inferior at the primary end point at 48 weeks) (Lennox *et al*. 2009; Rockstroh *et al*. 2013). - Equivalent to ATV/r and DRV/r (Superior to both drugs at the combined endpoint of tolerability and effectiveness) (Landovitz *et al*. 2014). - Not-inferior to DTG if the total (not stratified) population is considered; inferior to DTG in long term studies (96 weeks) in patients with baseline viremia >100.000 copies/ml (Raffi *et al*. 2013a; Raffi *et al*. 2013b).	- Improved lipidic profile compared to PI/r and EFV (Lennox *et al*. 2009; Rockstroh *et al*. 2013; Ofotokun *et al*. 2014). - Lower risk of BMD reduction compared to ATV/r and DRV/r (if used in association with TDF) (Brown *et al*. 2014). - No food-drug interactions reported. - No CYP3A4-related pharmacological interaction. - Extensive clinical use.	- Twice a day regimen - Co-formulations with other ARVs are not available. - Evaluated in association with TDF/FTC. Association with ABC/3TC has been evaluate only in one - RCT (Raffi *et al*. 2013a; Raffi *et al*. 2013b). - Increased risk of resistance mutations at failure compared to IP/r or DTG (Raffi *et al*. 2013a; Raffi *et al*. 2013b; Landovitz *et al*. 2014). - Increase risk of elevated levels of creatinkinase, myopathy e rhabdomyolysis (Lee *et al*. 2013) (Merck Sharp & Dohme Corp 2015). - HSR has been reported (including SJ syndrome) (Merck Sharp & Dohme Corp 2015). - Antacids containing metals significantly decrease RAL plasma levels. Co-administration of aluminum or magnesium hydroxide-containing antacids and RAL is not recommended. CaCO3 antacids are recommended as an alternative.

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ARVs class	*Drug(s)*	*Evidences of efficacy deriving from RCT*	*Advantages*	*Disadvantages*
INI	EVG/ COBI	- Evaluated in comparative studies against only EFV and ATV/r. - Not inferior to EFV (DeJesus *et al*. 2012; Sax *et al*. 2012; Clumeck *et al*. 2014; Wohl *et al*. 2014) and ATV/r (in association with TDF/FTC) (DeJesus *et al*. 2012; Clumeck *et al*. 2014).	- Once a day regimen. - Available in co-formulation and STR with TDF/FTC. - Improved lipidic profile compared to EFV and ATV/r (associated to TDF/FTC) (DeJesus *et al*. 2012; Sax *et al*. 2012; Clumeck *et al*. 2014; Wohl *et al*. 2014).	- Available in association with TDF/FTC only. - Contraindicated if CRCL <70 ml/min - Increased risk of resistance mutations at failure compared to PI/r or DTG (DeJesus *et al*. 2012; Sax *et al*. 2012; Clumeck *et al*. 2014; Wohl *et al*. 2014). Contraindicated in patients with impaired renal function (GFR <70 mL/min/1.73 m^2). - Use of ETG/COBI has been associated to an higher risk of kidney failure and proximal renal tubulopathy (DeJesus *et al*. 2012; Sax *et al*. 2012; Clumeck *et al*. 2014; Wohl *et al*. 2014). - COBI affects creatinine active tubular secretion and its use can increase serum creatinine and GFR without an effect on glomerular filtration (German *et al*. 2012). - Possible pharmacological interactions (COBI is a strong inhibitor of CYP3A4). - Co-administration of aluminium or magnesium hydroxide-containing products and ETG/COBI is not recommended since polyvalent cations might interfere with absorption. - Administration with food is recommended - Limited real life data available.
	DTG	- Evaluated in association both with TDF/FTC and with ABC/3TC. - Evaluated in comparative studies against all other recommended anchor drugs except RPV, ATV/r, and EVG/COBI. - Superior to EFV and DRV/r. (at primary endpoint at 48 weeks) (Walmsley *et al*. 2013; Clotet *et al*. 2014). - Not-inferior to RAL if the total (not stratified) population is considered; superior to RAL in long term studies (96 weeks) in patients with baseline viremia >100.000 copies/ml (Raffi *et al*. 2013a; Raffi *et al*. 2013b). - Demonstrated virological efficacy regardless of the associated drugs (TDF/FTC or ABC/3TC) and plasma HIV RNA at baseline.	- Once a day regimen. - Available in co-formulation and STR with ABC/3TC. - Risk of resistance mutations at virological failure similar to Pi/r and lower than NNRTIs and other INIs (Raffi *et al*. 2013a; Raffi *et al*. 2013b; Walmsley *et al*. 2013; Clotet *et al*. 2014). - Better tolerability compared with the majority of anchor drugs. - Improved lipidic profile compared to EFV e DRV/r (Walmsley *et al*. 2013; Clotet *et al*. 2014). - No food-drug interactions reported. - No reported CYP3A4-dipendent interaction.	- DTG affects creatinine active tubular secretion and its use might increase serum creatinine and GFR without an effect on glomerular filtration. - Co-administration of aluminium or magnesium hydroxide-containing products and DTG is not recommended since polyvalent cations might interfere with absorption. - DTG is a substrate of uridine diphosphate glucuronosyltransferase. - Limited real life data available.

compared to other molecules of the same drug class.

Randomized clinical trials which have been completed through the primary endpoint suggest that the combination PI/r/3TC/FTC might be graded as highly recommended [AI] in presence of NRTIs associated toxicity and moderately recommended [BI] to prevent NRTI associated toxicity.

Dual therapies lacking a PI/r are not recommended to date since clinical trials which evaluated these regimens lack the adequate robustness and their results are not encouraging in terms of efficacy.

Monotherapy (Tables 8, 9). Several studies have evaluated the switch from a standard therapeutic regimen to a monotherapy consisting of a PI/r. The rationale supporting these strategies

TABLE 7 - *Summary of rationale/advantages/disadvantages of dual therapy for treatment optimization.*

Class of optimization	*AIM*	*Potential advantages*	*Potential disadvantages*	*Rate of recommendation*	*Related literature*
From a combination of three drugs to a PI/r + NNRTI regimen (a)	Reduce/Prevent NRTI associated toxicity	Demonstrated virological efficacy in subjects not eligible for simplification to monotherapy	In case of virological failure, development of resistance towards the newly introduced therapeutic class. NNRTI associated toxicity	[CI]	(Negredo *et al*. 2009; Negredo *et al*. 2013)
From a combination of three drugs to DRV/r or LPV/r + RAL (b)	Reduce/Prevent NRTI associated toxicity	Demonstrated virological efficacy in subjects not eligible for simplification to monotherapy	Development of resistance towards the newly introduced therapeutic class (in case of virological failure); metabolic profile impairment(d)	[BI] in presence of NRTI toxicity or [CI] as a preventive measure	(Ofotokun *et al*. 2012; Nishijima *et al*. 2013; Madeddu *et al*. 2014; Van Lunzen *et al*. 2014)
From a combination of three drugs to a PI/r + 3TC or FTC (c)	Reduce/Prevent NRTI associated toxicity	Demonstrated virological efficacy in subjects not eligible for simplification to monotherapy	Increased toxicity	[AI]] in presence of NRTI toxicity (excluding 3TC/ FTC) or [BI] as a preventive measure	(Di Giambenedetto *et al*. 2013; Borghetti *et al*. 2014; Gianotti *et al*. 2014a; Perez-Molina *et al*. 2014)

a) Few clinical trials evaluated this regimen testing an association no longer in use in clinical practice (LPV/r + NVP). Based on the known pharmacokinetic properties, it is reasonable to expect similar results for the association DRV/r + ETR or RPV, however no robust experimental data for this association have been produced so far. Similarly, there is no clear evidence supporting the reduction of NRTI associated toxicities. b) KITE study: clinical study involving 60 subjects with suppressed HIV replication, randomized (2:1) to switch to LPV/r 400/100 mg BID + RAL 400 mg BID or to continue on previous cART regimen. At week 48, 92% of the LPV/r + RAL arm and 88% of the control arm had maintained HIV RNA>50 copies/ml. Patients who switched to LPV/r + RAL showed a significantly higher triglyceridemia. SPARE study: 58 patients with plasma HIV RNA<50 copies/ml in treatment with LPV/r+TDF/FTC at the moment of enrollment, randomized (1:1) to switch to DRV/r + RAL or to continue the previous cART regimen. 100% of patients included in arms showed virological suppression at week 48; Tenofovir tubulopathy showed significant improvement in the RAL+DRV/r compared with both LPV/r+TVD HARNESS study: 109 patients with virologic suppression were randomized (2:1) to switch from a triple-drug regimen including 2 NRTIs to ATV/r 300/100mg once daily +RAL 400 mg twice daily. At week 24, plasma HIV RNA below the limit of detection occurred in 80.6% in the ATV/r + RAL arm and in 94.5% of patients in the ATV/r + TDF/FTC arm. At 48 weeks (secondary endpoint) virological suppression occurred in 69.4% and 86.5% of patient, in the ATV/r + RAL arm and in the ATV/r + TDF/FTC arm, respectively. A retrospective study (ICONA) considering 101 patients with suppressed viremia who started a new therapeutic regiment with DRV/r + RAL estimated a relatively low risk (13% at 1 year, 16% at 2 years) of therapeutic failure (virological failure or discontinuation due to toxicity). Risk of virological failure was slightly higher for the patients with higher baseline HIV RNA levels. Reductions in NRTI associated toxicity were not demonstrated. c) SALT study: 286 patients with HIV RNA of less than 50 copies/ml for at least 6 months were randomized (1: 1) to dual treatment with ATV/r+3TC or triple treatment ATV/r+2NRTIs . At week 48 (primary endpoint) virological suppression (HIV RNA<50 copies/ml) was observed in 83% of patients in the ATV/r+3TC arm and 78.4% of patients in the ATV/r+2NRTIs arm demonstrating non-inferiority (difference: +5.2%; 95%CI 15.2% -4.8%). In the ATLAS-M study, the interim analysis (24 weeks) performed on 124 patients randomized to switch to ATV/r+3TC or to maintain the original three-drug regimen, showed 5.7% treatment failure in the ATV/r+3TC arm and 14.1% in the ATV/r + 2NRTIs arm. Treatment with ATV/r + 3TC was associated to an improved recovery of CD4 T cell counts and kidney function, and with a slight impairment of the lipidic profile. Finally, in the ATLAS study, among 40 patients with plasma HIV RNA <50 copies/ml switching from ATV/r + 2NRTI to a treatment with ATV/r + 3TC, one had virological failure and four patients reported kidney colic pain. Kidney function was improved overall, however the study reported an impairment of the lipidic profile.
Study OLE: HIV infected patients with <50 copies/ml for at least six months on triple therapy with LPV/r + 3TC or FTC and a third nucleos(t)ide were randomized (1:1) to switch to DTG with LPV/r and 3TC or continue triple therapy. Dual therapy regimen proved to be not inferior to triple therapy, with three virological failures for each arm, similar rate of adverse effects and slight impairment of lipidic profile in the dual therapy regimen arm. Two small retrospective studies have recently shown that optimization using DRV/r + 3TC or FTC does not involve a significant risk of virological failure, while being associated to an improvement of kidney function (in particular in patients under TDF treatment); impairment of lipidic profile was observed also in these studies. d) The switch to the combination ATV/r + RAL is associated with a higher risk of virological rebound and therefore is not recommended.

is to limit or prevent NRTI associated toxicity while, at the same time, reducing the treatment costs.

The preliminary results of the biggest RCT evaluating monotherapy efficiency have been recently published (PIVOT study, including 587 patients). The aim of this study was to show the non-inferiority 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 avail-

able 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 (return to NRTI based regimen was considered assimilate to 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%).

Several different variables have been investigated in randomized, observational, and meta-analysis studies as possible predictors of virological failure after switch to PI/r monotherapy. Low nadir CD4 T cell count, low therapy ad-

TABLE 8 - *Summary of rationale/advantages/disadvantages of monotherapy for treatment optimization.*

Class of optimization	*AIM*	*Potential advantages*	*Potential disadvantages*	*Rate of recommendation*	*Related literature*
From dual or triple therapy to LPV/r 400/100 mg BID (a)	Reduce/Prevent NRTI associated toxicity	Favourable cost-effectiveness ratio	Increase pill burden except for patients coming from a LPV/r + 2NRTI regimen; adverse gastro enteric events; and increased long-term cardiovascular risk; lower virological efficacy; unclear results concerning virological efficacy in HIV sanctuaries, contraindicated in HBsAg positive patients	[AI] in presence of NRTI toxicity or [CI] as a preventive measure	(Cameron *et al*. 2008; Arribas *et al*. 2009; Bierman *et al*. 2009; Pulido *et al*. 2009; Gutmann *et al*. 2010; d'Arminio Monforte *et al*. 2014; Gianotti *et al*. 2014b; Pinnetti *et al*. 2014)
From dual or triple therapy to DRV/r 800/100 mg QD or DRV/r 600/100 mg BID (b)	Reduce/Prevent NRTI associated toxicity	Favourable cost-effectiveness ratio	Unclear results concerning virological efficacy in HIV sanctuaries, contraindicated in HBsAg positive patients	[AI] in presence of NRTI toxicity or [CI] as a preventive measure	(Gianotti *et al*. 2014b; Pinnetti *et al*. 2014) (Arribas *et al*. 2012; Valantin *et al*. 2012; Geretti *et al*. 2013; Antinori *et al*. 2014)
From dual or triple therapy to ATV/r 300/100 mg QD (c)	Reduce/Prevent NRTI associated toxicity	Favourable cost-effectiveness ratio	Lower virological efficiency, in particular in HCV co-infected patients with baseline plasma HIV RNA >100,000 copies/ml. Unclear results concerning virological efficacy in HIV sanctuaries, contraindicated in HBsAg positive patients	[AI] in presence of NRTI toxicity . Not recommended as preventive measure	(Swindells *et al*. 2006; Karlstrom *et al*. 2007; Spagnuolo *et al*. 2014)

a) Studies involving the switch to LPV/r provided heterogeneous data, depending on trial design and type of statistical analysis. However, these studies have shown that in some cases virological non inferiority compared to triple therapy was not achieved, that primary mutations conferring resistance to PI were present at virological failure, and that reintroduction of the two NRTIs resulted in suppression of viremia in almost all the cases of virological failure. Among the factors which can predict failure, some authors have identified low nadir CD4 T cell count, reduced adherence to therapy, levels of HIV DNA (no predictive threshold was identified), absence of LPV/r in the previous regimens, and a short virological suppression interval before the switch. HCV coinfection does not correlate with virological failure. In the PRIMO study, administration of LPV/r 800/200 mg twice a day has been associated with an higher risk of virological failure compared to the triple regiment (PI/r + 2NRTI) and is therefore contraindicated. b) The clinical trials MONET and PROTEA evaluated the switch to DRV/r at 800/100 mg dosage once a day, whereas the MONOI study investigated the 600/100 mg dosage once a day. In MONET and MONOI, virological non inferiority compared to control regimen (DRV/r + 2NRTI) at 48 weeks was achieved. In the MONOI study, non inferiority was achieved in *per protocol* analysis, but not in the intent -to-treat analysis, even if 96weeks after switching non inferiority was confirmed in all the analysis. In the MONET trial non inferiority was determined using a different type of analysis, but was not confirmed in the main analysis (ITT, TLOVR, Switch=Failure) at 96 weeks when non inferiority was maintained only if patient who reverted to a standard triple therapy were not included in the failed patient group. This data is confirmed at 144 weeks and underlines how HIV/HCV co-infection contributes to virological failure of DRV/r based monotherapy. In the PROTEA study, switch to DRV/r at 800/100 mg/day did not meet criteria for non inferiority in the general analysis (-8.7%; 95% CI -1.8% -15.5%), whereas in a post-hoc analysis a difference in efficacy between DRV/r and the control arm was observed only in patients with a CD4 T cell nadir lower than 200 cells/µl. In the same study, no difference between treatment groups was observed i terms of neurocognitive performances. No differences were observed in the subset of HCV co-infected patients included in the study. Results of the PIVOT study (see also general introduction) regard mainly DRV/r monotherapy since this therapeutic regimen was used in 80% of study participants. c) Since 2006 contrasting data deriving from non comparative studies were made available. The sole randomized clinical study lasting 96 weeks (MODAt) was interrupted for virological inferiority compared to triple therapy at week 48; long term analysis at week 96 did not demonstrated non inferiority (64% efficacy in the ATV/r arm vs 63% in ATV/r + 2NRTI arm, +1.3%; 95% CI -17.5% 20.5%). Higher risk of virological failure in HCV co-infected patients and patients with baseline plasma HIV RNA >100.000 copies/ml; monotherapy showed a better safety profile, but needs to be evaluated in long-term therapies.

TABLE 9 - *Summary of rationale/advantages/disadvantages of monotherapy, fixed dose combination and single tablet regimens for treatment optimization.*

Class of optimization	*AIM*	*Potential advantages*	*Potential disadvantages*	*Rate of recommendation*	*Related literature*
From NVP BID to RPV (a)	Improve adherence		Slight reduction of eGFR (uncertain clinical relevance)	[BIII]	(Allavena *et al*. 2014; Mora-Peris *et al*. 2014)
From EFV to RPV (b)	Reduce/ prevent toxicity	Lower metabolic impact and improvement of EFV associated neurological symptoms	Slight reduction of eGFR (uncertain clinical relevance)	[BIII]	(Mills *et al*. 2013b)
From NNRTI to EVG/COBI/ FTC/TDF (c)	Reduce/ prevent toxicity	Lower incidence of adverse events targeting SNC; slight metabolic improvement	Slight reduction of eGFR (uncertain clinical relevance)	[AI]	(Pozniak *et al*. 2014)
From PI/r to EFV (d)	Reduce/ prevent toxicity	Available in co-formulation; reduced gastrointestinal adverse effects	Increased incidence of adverse events, in particular targeting DN. Lower genetic barrier	[AI]	(Martinez *et al*. 2007; Dejesus *et al*. 2009)
From PI/r to NVP (d)	Reduce/ prevent toxicity	Reduced gastrointestinal adverse effects and lower metabolic impact	Short-term skin and liver toxicity. Lower genetic barrier	[AI]	(Martinez *et al*. 2007; Dejesus *et al*. 2009)
From PI/r to TDF/FTC/RPV (e)	Reduce/ prevent toxicity	Reduced gastrointestinal adverse effects and lower metabolic impact	Lower genetic barrier	[AI]	(Palella *et al*. 2014)
From PI/r to RAL (f)	Reduce/ prevent toxicity	Reduced gastrointestinal adverse effects and 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; start at least 6 weeks after achieving virological suppression	[BI]	(Eron *et al*. 2010; Martinez *et al*. 2010; Curran *et al*. 2012)
From PI/r to EVG/ COBI/FTC/TDF (g)	Reduce/ prevent toxicity	Improved virological suppression	Lower genetic barrier (?)	[AI]	(Arribas *et al*. 2014)

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. b) In a single centre open-label non comparative study evaluating 49 patients treated with EFV/FTC/TDF (STR), 93% of patients maintained virological suppression after switching to RPV/FTC/TDF (STR). Two patients reported virological failure. c) Virological non-inferiority (93% vs 88%) at week 48 was demonstrated in a randomized clinical trial enrolling 434 patients switching to STR containing EVG/COBI/FTC/TDF. The simplified arm showed less SNC abnormalities, a tendency to eGFR increase, and a reduction of metabolic impact compared with the control arm (NNRTI based therapy). d) 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. e)In the SPIRIT multicentre clinical trial, 476 virologically suppressed HIV patients were randomized (2:1) to switch to TDV/FTC/RPV immediately or at week 24. Through 24 weeks, switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs and resulted in a slight increase of eGFR and in an improvement of lipidic profile. At week 48, 89.3% of patients in the simplification arm maintained virological suppression. f) Non inferiority was not observed in a randomized clinical trial evaluating the switch from LPV/r to RAL in virologically suppressed patients (SPIRAL). The factors mainly associated with virological failure were the presence of previous failures and thus, likely, presence of mutations conferring resistance to NRTI. A second randomized clinical trial 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, while in SPIRAL study use of RAL significantly reduced statin consumption and improved bone mineral density. g) A randomized clinical trial evaluating the effects of therapeutic simplification to a STR including EVG/COBI/FTC/TDF showed superiority in terms of viral suppression at week 48 compared to control group (antiretroviral therapy based on PI) (94% vs 87%).

herence, limited duration of either the previous antiretroviral treatment or the viral suppression were all associated with an increased risk of failure. The most accurate parameter predicting virological failure was nadir CD4 T cell count. Increased risk of failure was associated with nadir CD4 T cell counts <100 cells/μl in the OK-4 study, and to nadir CD4 T cell counts <200 cells/μl in the MOST and PROTEA studies. Is then advisable to consider a nadir CD4 T cell count above 200 cells/μl as the threshold to select HIV patients eligible for DRV/r or LPV/r monotherapy.

The association between failure to monotherapy and HCV was confirmed in the MODAT and MONET studies which evaluated the effect of switch to monotherapy with ATV/r and DRV/r, respectively. However, other studies such as the MONOI, PROTEA and PRIMO as well as the studies including LPV/r failed to identify this association and do not support the presence of HIV/HCV coinfection as a predictor of PI/r monotherapy response.

Additional factors which showed ability to predict virological failure only in some studies where higher level of basal HIV viremia (HIV-RNA >1 copy/ml o >5 copies/mL in MONOI e MONET studies, respectively) and basal HIV DNA levels (MONOI e MONET studies).

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 neurocognitive impairment and PI/r monotherapy. However the analysis of the two RCT (PIVOT and PROTEA) in which neurocognitive assessment was included in the trial evaluation scheme, did not confirm the existence of an increased risk of neurocognitive impairment during PI/r monotherapy. Additional observational studies, both cross-sectional and longitudinal, have further confirmed the latter finding ruling out the existence of a correlation between neurocognitive impairment and monotherapy.

Nevertheless, viral replication in CSF was observed in multiple clinical trials, although in a negligible fraction of patients [9 (1%) patients out of 800 switching to DRV/r or ATV/r monotherapy as reported in a recent meta-analysis]. In the study PROTEA, virological rebound in CSF was observed in 1 out 21 patients in the DRV/r monotherapy arm and in 0 out 19 patients in the DRV/r + 2NRTIs arm.

Switch to LPV/r BID o DRV/r QD o BID might be recommended in patients experiencing NRTI toxicity [AI] or represent a therapeutic option to prevent NRTI related toxicity [CI]. To be eligible for switch to LPV/r od DRV/r monotherapy patients should be already in treatment with PI, with no clinical history of virological failure during PI treatment, show no evidence of mutation conferring resistance to PI, have plasma HIV RNA <50 copies/ml for at least 12 months, and nadir CD4 T cell count >200 cells/μL. Monotherapy using ATV/r might be considered in patients experiencing NRTI related toxicity who are not eligible for DRV/r or LPV/r combination [BI].

Data deriving from RCT indicate HIV/HCV coinfection is a predictive factor for virological failure in patients switching to monotherapy with ATV/r, but not with LPV/r while for DRV/r results are controversial Nevertheless, in absence of more robust data, PI/r monotherapy does not guarantee a sufficient levels of efficacy and safety in HIV/HCV coinfected individuals.

Regardless of the specific group of patients, for patients switching to Pi/r monotherapy a close monitoring, including HIV viral load monitoring every three months, is mandatory in order to rapidly identify possible virological failure and to implement strategies for checking patient's therapy adherence [AIII]. At virological rebound, defined as two consecutive HIV RNA measurements above 50 copies/ml in plasma, it is recommended to perform a genotypic resistance test [AIII], possibly also on DNA, and the return to the traditional triple therapy [AIII].

Pill burden reduction: Fixed dose combinations (FDC), once daily regimens, and single tablet regimens (STR) are therapeutic resources developed in order to reduce regimen complexity and promote adherence in clinical practice.

- FDC provide fixed concentrations for drugs combinations which are preferred over non-standardized combinations.
- Once daily regimens: daily intake (QD) (opposed to twice a day regimens - BID).

- Single tablet regimens: co-formulations of multiple drugs in the same tablet.

Switching from PI to a different antiretroviral class (NNRTI or INI), i.e. from a regimen with a very high genetic barrier to a regimen with a minor genetic barrier, is recommended to improve therapy tolerability.
However this therapeutic choice is appropriate only for patients who have never experienced virological failure or assumed NRTI at suboptimal concentrations or presented mutation associated with NRTI resistance (and NNRTI if the switch involves this class of drugs) [AI].
Moreover, in case of a new regimen including RAL, a minimum of 6 months of virological suppression are required to switch.

TABLE 10 - *Strategic actions to enhance retention in care.*

General principle	*Intervention*	*Rate of recommendation*	*Related literature*
Retention in care is associated with improved long-term survival.	- Inform the patients about the advantages of antiretroviral therapy adherence and regular counselling. - Monitor retention in care for all the individuals in the follow-up population.	[AII]	(Hall *et al*. 2013; Crawford 2014; Crawford *et al*. 2014; Nachega *et al*. 2014; Yehia *et al*. 2014)
Retention in care is essential in order to prevent virological failure, achieve immunological recovery and reduce the risk of transmission.	At each visit: - Define, together with the patient, the diagnostic work up and therapeutic course. - Verify the patient's comprehension. If scheduled appointments are missed. - Identify reasons for missed appointments. - Develop, together with the patient, a strategy to remove structural barriers preventing appointment adherence. - Multidisciplinary education and counselling intervention approaches are recommended.	[AII]	(Gardner *et al*. 2011; Horberg *et al*. 2013; Gardner *et al*. 2014)
Retention in care is achieved through the co-operation of a group of different professional figures.	- Integrate competencies and experiences from different professional figures. - Adopt an empathic approach. - Customize interventions based on the specific needs of the patient. - Reinforce motivation and involve the patient in the establishment of the therapeutic course.	[BII]	(Gardner *et al*. 2011; Hall *et al*. 2013; Horberg *et al*. 2013; Gardner *et al*. 2014)
The highest risk of loss at follow up is occurs during the following periods: - The observational period between diagnosis and start of therapy. - The first months after therapy start.	- Optimize HIV counselling starting from the diagnosis of HIV infection. - Provide the necessary information before starting antiretroviral therapy. - Tune the diagnostic work up and the therapeutic flow to the different phases of infection (i.e. schedule more frequent appointments at the beginning of cART treatment). - Provide psychological support.	[BII]	(Gardner *et al*. 2011)

Risk factors associated with poor retention in care are more common in some groups of patients.	- Increase awareness for the following situations:
	  - Young age.
	  - Drug or alcohol addictions.
	  - Psychiatric diseases.
	  - Previous incarceration.
	  - Transgenders.
	- Collaborate with complementary health care professionals.
		[CIII]	(Crawford *et al*. 2014)

The current methodological approach to determine retention in care is not standardized and needs to be adjusted to the specific clinical setting.	- Record missed appointments. - Check appointment adherence, regular testing, and medication pick up.	[AII]	(Brennan *et al*. 2014)

TABLE 11 - *Interventions to enhance retention in care and re-linkage.*

General principle	*Intervention*	*Rate of recommendation*	*Related literature*
Improving health care practitioner-patient relationship increases the chances of retention in care.		[BI]	(Brennan *et al*. 2014)
Nurses might play a fundamental role for retention in care.	- Educate nurses and health personnel involved in the everyday activity in health care institutions on the importance of antiretroviral therapy adherence. - Inform the patient on the steps of the diagnostic and therapeutic process. - Check adherence to therapy. - Implement an appointment reminder system.	[BI]	(Raper 2014)
Relationships with health care professionals, and social support networks promote engagement in care.	- For patients displaying psychological distress due to social isolation, linkage with associations of people living with HIV is recommended in order to provide them assistance during the initial stages of the therapeutic process. - Promote communication and understanding. - Decrease social isolation.	[BI]	(Thompson *et al*. 2012; Stricker *et al*. 2014)
Appointment reminder system.	- Call (or email/text) the patient few days before the next scheduled appointment.	[BI]	(Thompson *et al*. 2012)
Develop an active program for re-linkage to care for the patients who are lost to follow up.	- Get in touch with the patient. - Identify and propose a strategy to overcome the barriers preventing retention in care. - Define, together with the patient, the diagnostic work up and therapeutic course. - Offer psychological support to the patient (medical specialists and structured groups programs).	[CIII]	(Thompson *et al*. 2012)
Reduce waiting times for appointments.	- Provide the opportunity to perform diagnostic tests or visits outside the scheduled appointments. - Schedule the next appointment at the end of the visit.	[CIII]	(Thompson *et al*. 2012; Stricker *et al*. 2014)

RETENTION IN CARE

Retention in care is one of the fundamental steps included in the *continuum of care*, a concept recently introduced in the HIV field to describe the process from diagnosis of a new infection (HIV testing), to connection with a health care provider (linkage of care), start and adherence to antiretroviral therapy (engagement in care) and achievement and maintenance of viral suppression.
Similarly to what observed for other chronic diseases, continuum of care for HIV:

- Is a fundamental factor to achieve and maintain the therapeutic goals, necessary to guarantee patients quality of life (Nachega *et al.* 2014).
- It can be considerate a surrogate marker to measure the quality of health care assistance (Crawford *et al.* 2014).
- In the context of HIV infection, continuum of care is a powerful tool to reduce new infections and control the spread of epidemics (Crawford 2014).

Retention in care of HIV infected persons under antiretroviral treatment is strongly dependent on the creation of a favourable environment where all the health care players work cooperatively to successively connect and actively engage HIV patients.
In this process, providing an emphatic approach and the ability to tailor antiretroviral regimen in view of the specific situation of each patients are favourable elements to achieve retention in care (Tables 10, 11).

Estimates for continuum in care in Italy (2012)

A model recapitulating the projections for the continuum in care in Italy has been recently developed 2012 (Girardi 2014).

The number individuals living with HIV in Italy equals to 130,000, of whom 15% is not aware of his/her seropositive status (Mammone *et al.* 2014). Of the 110,000 diagnosed individuals, 15% is not retained to care (Lazzaretti *et al.* 2012), thus the total number of HIV infected persons connected to health care providers is 94000. Of them, about 13% is not under treatment (Raimondo *et al.* 2013). Based on epidemiological studies performed in Italy (ICONA Foundation - Italian Cohort Naive Antiretrovirals), it might be estimated that 73,000 of the 82,000 individual in therapy have reached viral suppression.

As a consequence, in Italy, only 54% of persons living with HIV has achieved virological suppression.

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

In all the patients with chronic hepatitis C infection the opportunity to implement a pharmacological treatment based on direct antiviral drugs alone or in combination with pegylated interferon and ribavirin must be considered (Table 12) (Association for the Study of Liver Diseases (AASLD) and International Antiviral Society-USA (IAS-USA); European AIDS Clinical Society (EACS) 2014; European Association for the Study of the Liver 2014). If efficacy is similar, therapies interferon free must be preferred (European Association For The Study Of The Liver 2014). Tables 13 to 16 provide an overview of the therapeutic indications for different drugs and groups of patients, please refer to Table 17 for the rating schemes of levels of recommendation and degree of evidence for HCV studies.

TABLE 12 - *Indications for treating HIV/HCV coinfection.*

HCV coinfection should be eradicated in all HIV infected individuals for the following reasons:
- High mortality due to hepatocellular carcinoma and unbalanced cirrhosis deriving from a rapid progression of the hepatic disease (Ioannou *et al*. 2013).
- Negative impact of the HCV infection on:
a) Kidney function (Ioannou *et al*. 2013) and, in general, on mortality not associated to hepatic disease (Grint *et al*. 2014);
b) Increase of CD4 T cell count during cART (Potter *et al*. 2010).
- Possible negative impact of HCV on:
a) HIV disease progression even in presence of cART (De Luca *et al*. 2002);
b) Osteoporosis (Lo Re *et al*. 2012);
c) Cardiovascular disease (Butt *et al*. 2014);
d) Onset of diabetes (Howard *et al*. 2010).
HCV eradication is associated with a decreased incidence of hepatic failure and mortality mainly in patients with advanced liver disease (Berenguer *et al*. 2012), but also in patients with moderate fibrosis (Berenguer *et al*. 2014).

Rate of recommendation	*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 con FIB4 >3.25)§
	Patients with cryoglobulinemia and symptomatic vasculitis.
	Patients with nephrotic syndrome or membranoproliferative glomerulonephritis non HIV associated
Very high [AII]	Patients with moderate fibrosis (histology: >F1 METAVIR o S2 ISHAK and/or Stiffness >7.1 as determined by fibroscan and/or FIB4 >1.45) (Berenguer *et al*. 2014)
High [AII]	All remaining patients co-infected with HIV/HCV (Grint *et al*. 2014)

§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 (European Association for the Study of the Liver 2014).

TABLE 13 - *HCV therapy guidelines for HIV/HCV co-infected patients (HCV genotype 1, 5, 6)*

Stage of the disease[§]	*Response to previous PR therapy*[#]	*PR*[a]	*PR*[a] *BOC*[c]	*PR*[a] *SIM*	*PR*[a] *DCV*	*PR*[a] *SOF*	*SOFO R*	*SOF SIM +R*[g]	*SOF DCV +R*[g]	*SOF LDV +R*[g]	*3D + R*[g]
Non cirrhosis	Never treated Relapsing	B-I in RVR[b]/ Not recommended		B-I in HCV G1bA-II se RVR[bcef]	Not recommended	A-II/B-II[d]	B-I	A-II[l]	A-II	A-II	A-II
	Not responding	Not recommended		Not recommended		C-II[d]	Not recommended	A-II/B-II in PI experienced anti HCV	A-III	A-II	A-II
Cirrhosis	Never treated Relapsing	Not recommended		Not recommended		B-II in HCV G1[a] C-III in HCV G1[bd]	C-III	B-II[l]	A-IV	A-II	A-II
	Not responding	Not recommended		Not recommended		C-II	Not recommended	B-II / C-II in PI experienced anti HCV[l]	A-IV	A-II	A-II
Unbalanced Cirrhosis	Contraindicated	Contraindicated		Contraindicated		Contraindicated	C-III	Not recommended in patients with hepatocellular liver failure	A-IV	B-II	Not recommended

TABLE 14 - *HCV therapy guidelines for HIV/HCV co-infected patients (HCV genotype 2).*

Stage of disease[§]	*Response to previous PEG IFN + RBV therapy*[#]	*PR*[a]	*PR*[a]*+ SOF*[g]	*SOF + R (12-24 weeks)*
Non Cirrhosis	Never treated/Relapsing	C-I; B-I se RVR[b]	A-IV	A-II
	Not responding	Not recommended	B-IV	B-II
Cirrhosis	Never treated/Relapsing	C-I ; B-I se RVR[b]	A-IV	B-II
	Not responding	Not recommended	B-IV	C-III
Unbalanced Cirrhosis*			Not recommended	C-IV

Legend Table 13-16: Only few data are available concerning the efficacy against genotype 5 and 6, generally their response is considered similar to the one of HCV genotype 1 viruses. § Stage of the disease: Cirrhosis (Stiffness >12 and or histological staging F4 METAVIR or S4-5 Ishak). [#]Previous therapy: Naïve: patients who never used PR. Experienced (Exp) patients who were treated using PR.
Relapsing (Rel): patients with HCV RNA below the detection limit at the end of PR treatment cycle who relapsed afterwards. Non responders (NR): patients with detectable HIV RNA after PR treated (HCV RNA decrease lower than $2Log_{10}$ after 12 weeks). *Class B or C decompensated cirrhosis according to Child Turcotte Pugh classification. [a]Pegylated interferon is contraindicated in subjects intolerant to interferon in previous therapies and/or serum albumine <3.5 g/dL with PLT <100.000 and/or other contraindication as reported in the Summary of Product Characteristics (SCP). [b]RVR: HCVRNA <25 IU/ml after 4 weeks of therapy in combination with PR or with PR + Boceprevir. [c]PR + BOC or SIM Response Guided Therapy: see SCP. [d]PR + SOF: B in HCV G1 a naive C in HCV G1b and experienced patients. [e]PR + SIM: Not recommended in HCV G1a harbouring the Q80K polymorphism. [f]PR + DCV Not recommended in HCV G1a. [g]Therapy indications for ribavirine are reported in the SCP.
[h]Treatments with SOF e DCV without ribavirine for 12 weeks has shown SVR <70% in cirrhotic HCV G3 experienced e naïve patients. Longer therapy (24 weeks) or combination with ribavirine (12 weeks) will likely increase SVR. [i]In a pilot study evaluating SOF e LDV without ribavirine for 12 weeks SVR was 89% in 28 non cirrhotic experienced patients and 73% in cirrhotic experienced patients. [l]Available data concerning SIM + SOF are mainly deriving from retrospective analysis of longitudinal cohorts or public available database. Predictive factors for failure are: hepatic cirrhosis (stronger effect if advanced), low albumin levels (albumin <3.5 g/dl o PLT <75.000/mm3 o previous hepatic disease), infection with HCV genotype G1a and previous failure to triple therapy with PR + BOC or TEL. [m]Treatment with SIM is not indicated in class CTP, B or C decompensated hepatic cirrhosis. SIM is a therapeutic option, if no other drug is available, for treatment of class B decompensated hepatic cirrhosis with controlled ascites if indices of liver function (indirect bilirubin, serum albumin, INR) are within the normal range.

TABLE 15 - *HCV therapy guidelines for HIV/HCV co-infected patients (HCV genotype 3).*

Stage of disease[§]	*Response to previous PEG IFN + RBV therapy*[#]	*PR*[a]	*PR*[a] *+ SOF*	*SOF + R (24 weeks)*	*DCV + SOF ± R*[gh]	*SOF LDV FDC*[gi]
Non Cirrhosis	Never treated/Relapsing	C-I/ B-I if RVR[b]	A-IV	A-II	A-III (12 weeks)	A-IV
	Not responding	Not recommended	B-IV	A-II	A-III (12 weeks no R)	B-IV
Cirrhosis	Never treated/Relapsing	C-I/B-I se RVR[b]	Data not available	A-IV	C-IV (12 weeks)	A-IV
	Not responding	Not recommended	B-IV	C-III	C-III (12 weeks no R)	C-IV
Unbalanced Cirrhosis		Not recommended		C-IV	B-IV	C-IV

TABLE 16 - *HCV therapy guidelines for HIV/HCV co-infected patients (HCV genotype 4).*

Stage of disease[§]	*Response to previous PEG IFN + RBV therapy*[#]	*PR*[a]	*PR*[a] *+ SOF*	*PR*[a] *+ SIM*[c]	*PR*[a] *+ DCV*[c]	*SOF + R (24 weeks)*	*SOF-SIM + R*	*DCV + SOF + R*[g]	*SOFLDV FDC+R*[g]	*Ombitasvir/ Paritaprevir/ Ritonavir FDC*[g]
Non Cirrhosis	Never treated/ Relapsing	BI in RVR[b]	A-III	B-III	B-III	A-III	A-IV	A-IV	A-IV	A-III
	Not responding	Not recommended	Data not available	C-III	Data not available	A-III	A-IV	A-IV	A-IV	A-III
Cirrhosis	Never treated/ Relapsing	Not recommended	A-IV	C-IV	B-.IV	A-IV	A-IV	A-IV	A-IV	Data not available
	Not responding	Not recommended	Data not available	C-IV	Data not available	B-IV	A-IV	A-IV	A-IV	Data not available
Unbalanced Cirrhosis*	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	B-IV	Not recommended in patients with hepatocellular liver failure[m]	A-IV	A-IV	Not recommended

TABLE 17 - *Rating scheme for degree of recommendation (A) and level of evidence (B) in HIV/HCV coinfected patients.*

	Degree of recommendation	
Cumulative efficacy	A	>90%.
	B	80-90%.
	C	<80%.
	Not recommended	Not recommended if alternative treatments are available
	Data not available	Limited clinical data available
Level of evidence	I	Data from >100 HIV infected patients.
	II	Data from >100 HIV infected and uninfected patients
	III	Dati from <100 HIV infected and uninfected patients
	IV	Anecdotical data

List of abbrevations

3D: ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir (Abbvie); 3TC: lamividuine; ABC: abacavir; ATV/r: ritonavir boosted atazanavir; ARV: antiretroviral drugs; BD: twice a day (bis in die); BMD: bone mineral density; BOC: Boceprevir; cART: combined antiretroviral therapy; COBI: cobicistat; CRCL: creatinine clearance; CSF: cerebrospinal fluid; DCV: Daclatasvir; DTG: dolutegravir; DRV/r: ritonavir boosted darunavir; EFV: efavirenz; EVG: elvitegravir; FDC: fixed dose combinations; FTC: emitricitabine; GFR: glomerular filtration rate; INI: integrase inhibitors; LDV: Ledipasvir; LDR: Less Drug Regimen; LPV/r: ritonavir boosted lopinavir NRTI: nucleoside reverse transcrip-

tase inhibitor; HSR: hypersensitivity reactions; NRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; N(t)RTs: nucleoside/nucleotide reverse transcriptase inhibitors; NVP: nevirapine; PR Pegylated Interferon + Ribavirine; PI/r: ritonavir boosted protease inhibitor; QD: once a day (quaque die); R: Ribavirine; RAL:raltegravir; RCT: randomized clinical trials; RPV: rilpivirine; RTV: ritonavir; SIME: simeprevir; SOF: sofosbuvir; STR: single tablet regimens; SVR: sustained virological response; TDF: tenofovir disoproxil fumarate.

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