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FULL PAPER

Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. Update 2016

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SUMMARY

The Italian Society of Infectious and Tropical Diseases (SIMIT) of the Technical Health Committee, Ministry of Health (Sections L and M) of Italy have supported recommendations for the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons. This publication summarizes the latest updates to the 2016 version of the Italian Guidelines for the management of HIV-1 infected patients and the use of antiretroviral drugs. In particular, new recommendations were released concerning the following topics: estimate of the HIV continuum of care in Italy, optimal timing and preferred drug combinations for starting antiretroviral therapy, treatment optimization, and pre-exposure prophilaxis (PrEP). For a complete review of clinical and therapeutic relevant topics we refer the reader to the extended version of the Guidelines.

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INTRODUCTION

This publication summarizes the latest updates to the 2016 version of the Italian Guidelines for the management of HIV-1 infected patients and the use of antiretroviral drugs (Antinori *et al*., 2016). In particular, in line with the previous guidelines released in 2016, this version include updated recommendations concerning the following topics: estimate of the continuum of care HIV positive individuals in Italy, optimal timing and preferred drug combinations for starting combined antiretroviral therapy (cART), treatment optimization, and pre-exposure prophilaxis (PrEP). Recommendations reported in 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. 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, impris-

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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.

onmnet) and transplants requiring special attention we refer the reader to the extended version of the the Guidelines (http://www.salute.gov.it/imgs/C_17_pubblicazioni_2442_allegato.pdf). 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.

Estimate of continum of care in Italy

According to the estimates based on the data collected by National Institute of Health (ISS) surveillance system and the Icona Foundation Cohort Study, the numbr of people living with HIV/AIDS in Italy is 134,000, 11% of these being not aware of their condition (Raimondo et al. 2016). Out of the 120,000 people who have been diagnosed with HIV, 15% have not been linked or maintained in care (Mammone *et al.,* 2016), leading to approximately 102,000 HIV-1 positive persons in care. Based on Icona Foundation Cohort data (ICONA 2015), it has been estimated that 83% of people diagnosed with HIV-1 and engaged in care are prescribed antiretroviral therapy and, of these, 87% have reached viral suppression (HIV-RNA < 50 copies/ml). As a result, in Italy, 74% of people living with HIV-1 (99,160 out of 134,000) is receiving cART, and 52% (69,680 out of 134,000) has achieved viral suppression. This estimate is consistent with those released by the AIDS Operational Centre of the ISS: according to the first, obtained applying the model developed by the Joint United Nations Program on HIV/AIDS (UNAIDS), in the year 2012, 123,000 people were living in Italy, with HIV, 93,000 of these being precribed cART (Camoni *et al.,* 2014). The second, performed over 170 clinical centers in the years 2012 and 2014, observed a 6.3% increase in the number of subjects diagnosed and engaged in care (100,049 *vs* 94,146) and an 11,4% increase in the number of patients who were prescribed treatment (91,916 *vs* 82,501) in 2014 compared to the 2012. Consistent with the recent data, in 2014, 87.7% of people receiving therapy achieved virological suppression (Raimondo *et al.,* 2014).

When to start antiretroviral therapy

The results of two randomized clinical trials (RCT) START and TEMPRANO (Insight Start Study Group *et al.,* 2015; Temprano ANRS Study Group *et al.,* 2015), emphasize the positive impact of early therapy on patients' global health, and the importance of proposing antiretroviral therapy to all HIV-1 infected individuals irrespective of their immune-virological status. Thus, the Italian panel strongly recommends initiation of cART in all HIV-1 infected adults regardless of their clinical status [AI]. Starting antiretroviral therapy should be related to both clinical benefit and effect of cART on reduction of HIV-1 transmission (Treatment as Prevention: TaSP).

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

In patients with opportunistic infections (OIs) for which a clinical benefit of prompt treatment initiation is established, treatment should be always strongly recommended and should be started immediately or at least within 2 weeks (*Pneumocystis jiroveci* pneumonia, progressive multifocal leukoencephalopathy, HIV wasting syndrome, HIV encephalopathy, *Cryptosporidium* or *Microsporidia enteritis*). On the contrary, cART initiation should be delayed for those OIs associated with an increased risk of detrimental effects related to immune reconstitution (criptococcal meningitis, tuberculous meningitis, CMV disease, atypical mycobacterial infection). In patients with tuberculosis, time of treatment initiation should be based on CD4 T cell count at diagnosis. Finally, cART should be started concomitantly to chemotherapy in all HIV-associated cancers.

Therapeutic regimens in naïve patients

In naïve 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 status and of its associated complications. Moreover, suppression of viral replication has been associated with positive effects on the community viral load, with 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 HIV positive 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 2*) and they all need to be considered in order to identify the best first regimen for a given patient.

The standard pharmacological treatment for HIV-1 patients naïve to therapy usually includes a combination of different antiretroviral drugs into the therapeutic regimen. Clinical trials, which provide fundamental information for the choice of therapy, are usually based on comparison of different regimens rather than single drugs. Nevertheless,

Table 2 - *Factors influencing the choice of the first line 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-1 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-1 infected patients.

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 regimen. For treatment initiation in acute or recent infections (e.g. within 6 months from possible viral transmission or acute retroviral syndrome), current HIV guidelines agree to recommend the use of an antiretroviral regimen demonstrated to be effective in presence of high viral load (HIV-RNA >100,000 copies/ml) [AII]. Despite the lack of evidences deriving from clinical trials, in patients with acute or recent infection carrying extremely high baseline viral loads (HIV-RNA >500,000 copies/ml), infectious diseases specialists might favor a transitory regimens with four different drugs including an integrase inhibitor and a protease inhibitor [CIII] until the resistance test (GRT) is not available.

Given the fact that current cART needs to be taken lifelong, it seems appropriate to implement the first regimen

Table 3a - *Antiretroviral regimens recommended for starting cART.*

Regimen	*Degree of recommendation/ Level of evidence*	*References*
Recommended regimen options (for all conditions)		
TDF/FTC + RAL	[AI]	Lennox *et al.,* 2009; Raffi *et al.,* 2013a; Raffi *et al.,* 2013b; Rockstroh *et al.,* 2013; Lennox *et al.,* 2014;
TAF/FTC + RAL	[AII]	Lennox *et al.,* 2009; Raffi *et al.,* 2013a; Raffi *et al.,* 2013b; Rockstroh *et al.,* 2013; Lennox *et al.,* 2014; Wohl *et al.,* 2015; Gallant *et al.,* 2016;
TDF/FTC/EVG/COBI	[AI]	DeJesus *et al.*, 2012; Sax *et al.,* 2012; Clumeck *et al.,* 2014; Wohl *et al.,* 2014; Squires *et al.,* 2015
TAF/FTC/EVG/COBI	[AI]	Sax *et al.,* 2015; Wohl *et al.,* 2016;
TDF/FTC + DTG	[AI]	Raffi *et al.,* 2013a; Raffi *et al.,* 2013b; Clotet *et al.,* 2014
TAF/FTC+DTG	[AII]	Data from studies in naïve patients are not available
ABC/3TC + DTG	[AI]	Raffi *et al.,* 2013a; Raffi *et al.,* 2013b; Walmsley *et al.,* 2013; Clotet *et al.,* 2014
ABC/3TC/DTG	[AI]	Raffi *et al.,* 2013a; Raffi *et al.,* 2013b; Walmsley *et al.,* 2013; Clotet *et al.,* 2014; Weller *et al.,* 2014
TDF/FTC/RPV (for patients with HIV-RNA <100.000 cp/ml and CD4 T cell count >200 cells/µl)	[AI]	Molina *et al.,* 2011; Cohen *et al.,* 2012; Cohen *et al.,* 2013a; Cohen *et al.,* 2014
TAF/FTC/RPV (for patients with HIV-RNA <100.000 cp/ml and CD4 T cell count >200 cells/µl)	[AII]	Data from studies in naïve patients are not available
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)	[AII]	Ortiz *et al.,* 2008; Molina *et al.,* 2010; Daar *et al.,* 2011; Soriano *et al.,* 2011; De Jesus *et al.,* 2012; Gallant *et al.,* 2013; Orkin *et al.*. 2013; Clotet *et al.,* 2014; Clumeck *et al.,* 2014; Lennox *et al.,* 2014; Mills *et al.,* 2015a
TAF/FTC+ATV+r or TAF/FTC+DRV+r (recommended in individuals with uncertain adherence or in patients who need to begin treatment before resistance testing results are available)	[AII]	Ortiz *et al.,* 2008; Molina *et al.,* 2010; Daar *et al.,* 2011; Soriano *et al.,* 2011; DeJesus *et al.,* 2012; Gallant *et al.,* 2013; Orkin *et al.,* 2013; Clotet *et al.,* 2014; Clumeck *et al.,* 2014; Lennox *et al.,* 2014; Mills *et al.,* 2015a
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]	Tashima *et al.,* 2014; Gallant *et al.,* 2015
TAF/FTC+ATV/COBI or TAF/FTC+DRV/COBI (recommended in individuals with uncertain adherence or in patients who need to begin treatment before resistance testing results are available)	[AII]	Tashima *et al.,* 2014; Gallant *et al.,* 2015

- 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 m2). Follow up data about tubular toxicity are limited. The combination EVG/COBI/FTC/TAF is a therapy option for patients with eGFR>30 ml/min.
- TAF/FTC backbone, once available, is to be considered the preferred choice in switching from TDF/FTC. TAF/FTC only for patients with eGFR>30 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.
- A TAF dose of 10 mg when used in combination with PK boosters (ritonavir or cobicistat) and 25 mg in unboosted regimens.
- 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. TAF/FTC/RPV is a therapy option for patients with eGFR >30 ml/min.
- Regimens including COBI are not recommended for treatment of pregnant patients.
- TAF/FTC/RPV is a therapy option for patients with eGFR >30 ml/min.

"/"=co-formulated; "+"=not co-formulated.

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).

Classification and degree of recommendation of cART regimens for the treatment of antiretroviral (ARV)-naïve patients

Recommended regimen options (for all conditions) (*Table 3a*)

The present document recommends, for all conditions, ten ARV regimens, eight based on integrase strand transfer inhibitors (INSTI) and two based on non-nucleoside reverse transcriptase inhibitors (NNRTI). The two recommended NNRTI-based regimens (tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)/emtricitabine (FTC)/rilpivirine (RPV) are indicated for cART 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 ten recommended regimens, the backbone nucleoside consists of a combination of FTC and TDF or TAF, except for the combination of abacavir (ABC) and lamivudine (3TC) that is recommended only in combination with the INSTI dolutegravir. Five out of these ten regimens are available as single tablet regimen (STR).

All these recommended regimens meet all the following criteria:

– Proven efficacy in RCT with sufficient potency (quality, numerosity, adequacy of control groups). In particular, recommended antiretroviral regimen must demonstrate non-inferiority over another already 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 3b*)

Eight different boosted-protease inhibitors (PI)-based regimens, including boosted atazanavir or darunavir (en-

Table 3b - *Alternative drugs combinations for first-line regimens.*

Regimen	*Degree of recommendation/ Level of evidence*	*References*
TDF/FTC/EFV or TDF/FTC+EFV	[BI]	DeJesus *et al.,* 2004; van Leth *et al.,* 2004; Gallant *et al.,* 2006; Arribas *et al.,* 2008; Riddler *et al.,* 2008; Sax *et al.* 2009; Post *et al.,* 2010; Lennox *et al.,* 2009; Daar *et al.,* 2011; Molina *et al.,* 2011; Sax *et al.,* 2012; Cohen *et al.,* 2013a; Nelson *et al.,* 2013; Rockstroh *et al.,* 2013; Walmsley *et al.,* 2013; Carey 2014; Cohen *et al.,* 2014; Wohl *et al.,* 2014
TAF/FTC+EFV	[BII]	Data from studies in naïve patients are not available
ABC/3TC+EFV (recommended if plasma HIV-1 RNA<100,000 copies/ml)	[BI]	Sax *et al.,* 2009; Post *et al.,* 2010; Daar *et al.,* 2011; Sax *et al.,* 2011
ABC/3TC+ATV/r (recommended if plasma HIV-1 RNA<100,000 copies/ml)	[BI]	Sax *et al.,* 2009; Daar *et al.,* 2011; Sax *et al.,* 2011
ABC/3TC+ATV/COBI (recommended if plasma HIV-1 RNA<100,000 copies/ml)	[BIII]	Sax *et al.,* 2009; Daar *et al.,* 2011; Sax *et al.,* 2011; Ramanathan *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-1 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 400mg 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 800/100 mg once a day.
- Risk of hyperbilirubinemia and hyperbilirubinemia-associated adverse effects needs to be considered before prescribing ATV/r and ATV/COBI.
- COBI is not recommended in patients with impaired renal function (GFR <70 ml/min/1.73m^2). Follow up data about tubular toxicity are limited.
- Regimens including COBI are not recommended for treatment of pregnant patients

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hanced by low-dose ritonavir or cobicistat), both combined to TDF/FTC or TAF/FTC as backbone nucleoside, are now recommended in particular conditions (patients with uncertain adherence, patients who need to begin treatment before resistance testing results are available, or for therapy initiation in pregnant women).
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.
For pro and cons of single drugs and drug combinations taking in account information concerning tolerability and toxicity, pharmacological interactions, formulations, posology, we refer the reader to the complete version of the Italian Guidelines.

Treatment optimization

Drugs reduction

The goal of this treatment scheme, named Less Drug Regimen (LDR), is to reduce the number of antiretroviral drugs included in a given regimen by applying an induction-maintenance therapeutic strategy. In the first phase, viral suppression is achieved trough a standard triple antiretroviral regimen. Then, once plasma viral load is not detectable anymore and immunoreconstitution is taking place (at least 6 months after achieving viral suppression), treatment could be safely 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 reducing possible drug-drug interactions is of particular interest given the aging of the

Table 4 - *Summary of rationale and advantages/disadvantages of dual therapy for treatment optimization.*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*References*
From a triple drug combination to ATV/r or ATV/c + 3TC	Reduce/ Prevent NRTI associated toxicity.	Virological efficacy non-inferior or superior (when switching from ATV/r+TDF/FTC) to triple drug combination prosecution.	Possible increased of PI associated toxicity	[AI] in patients experiencing toxicity induced by NRTIs different from 3TC/FTC or [BI] as a preventive measure	Perez-Molina *et al.,* 2015; Arribas *et al.,* 2015; Di Giambenedetto *et al.,* 2015
From a triple drug combination to DRV/r or DRV/c	Reduce/ Prevent NRTI associated toxicity.	Virological efficacy in subjects not eligible for simplification to monotherapy.	Possible increased of PI associated toxicity	[AI] in patients experiencing toxicity induced by NRTIs different from 3TC/FTC or [BI] as a preventive measure	Fabbiani *et al.,* 2016, Pulido *et al.,* 2016; Ciaffi *et al.,* 2016
From a triple drug combination to DRV/r or DRV/c + RPV (a)	Reduce/ Prevent NRTI associated toxicity		Limited long term data on efficacy. Possible development of NNRTI resistance (ETR included) in case of failure.	[BI/CI]	Maggiolo *et al.,* 2016
From a triple drug combination to DRV/r or DRV/c + RAL(b)	Reduce/ Prevent NRTI associated toxicity		Limited long term data on efficacy. Development of InSTI resistance (DTG included) in case of failure.	[CII]	Madeddu *et al.,* 2015; Calza *et al.,* 2016;
From a triple drug combination to DTG + RPV (c)	Reduce/ Prevent NRTI associated toxicity	PI toxicity savings	Limited long term data on efficacy. Possible development of InSTI and NNRTI resistance in case of failure	[CII]	Capetti *et al.,* 2016; Diaz *et al.,* 2016; Palacios *et al.,* 2016
From a triple drug combination to DTG + 3TC (d)	Reduce/ Prevent NRTI associated toxicity	PI toxicity savings	Limited long term data on efficacy. Possible development of InSTI (DTG included) and 3TC resistance in case of failure	[CII]	Maggiolo *et al.,* 2016; Baldin *et al.,* 2016; Reynes *et al.,* 2016

a): Randomized Pilot Study 1: 1, 60 patients with virologic suppression; virologic response at 48 weeks (snapshot analysis): 96.7% in the DRV/r +RPV *vs* 93.4% in the control arm (triple continuation PI+NNRTI) (Maggiolo *et al.*, 2016).

b): Two uncontrolled studies; the first including 82 patients in virologic suppression: 92.7% of patients with HIV-1 RNA <50 copies/mL at 48 weeks (Calza *et al.*, 2016); the second including 72 patients with virologic suppression; probability of treatment failure (virologic failure or discontinuation for any reason): 13% at 12 months, 22% at 24 months (Madeddu *et al*, 2015).

c): Evidences derived from three uncontrolled trials; In the first trial, which included 132 patients experiencing virological failure or virologic suppression; 98% of the 50 participants who reached week 48 had HIV-1 RNA<50 copies/mL (Capetti *et al.*, 2016); in the second trial, which included 38 virologically suppressed patients, 92% of participants maintained virologic suppression at 48 weeks (Diaz *et al.*, 2016). Finally, the third trial enrolled 104 patients, 80% them virologically suppressed at the time of trial initiation. Out of 85 patients who reached week 24 of follow-up, 97% had HIV-1 RNA <50 copies/ml (Palacios *et al.*, 2016).

d): Three uncontrolled trials; the first including 68 patients with virologic suppression; no virologic failure at 24 weeks (Maggiolo *et al.*, 2016); the second including 105 patients in virologic suppression; after 6 months 10 patients had discontinued treatment and 2 had a virologic failure (Baldin *et al.*, 2016); the third including 27 patients in virologic suppression; no virologic failure at 48 weeks (Reynes *et al.*, 2016).

HIV population and the use of concomitant medications for management of comorbidities.
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 4*)
Dual therapy regimens were developed with the aim of reducing or excluding the use of nucleoside reverse transcriptase inhibitors (NRTIs), since these drugs show high long-term toxicities. In particular, it has been suggested that the main benefit of dual therapy is the reduced risk of renal and bone toxicity usually associated with the use of TDF. Whether dual therapy will be less relevant after the introduction in clinical practice of TAF, which shows a better toxicity profile compared to TDF, remains to be assessed.
Since lopinavir/ritonavir based regimens are no longer recommended due to the high toxicity and low convenience (pill burden, gastro-intestinal tolerability and increased cardiovascular risk), the only PI-based regimens recommended are DRV and ATV-based dual combinations. The evidences for effectiveness of ATV/c or ATV/r+3TC and DRV/c or DRV/r+3TC are based on RCT and are sufficiently strong to allow a recommendation level [AI] for toxicity reduction and [BI] for NRTI toxicity prevention.
For DRV/c or DRV/r+RPV, although performed on a limited number of patients, randomized studies provide enough statistical power provide to grant a recommendation level [BI] for the reduction of toxicity and optional [CI] for the prevention of toxicity. The evidences for effectiveness of DRV/c or DRV/r+RAL are based on one study without control arm; however, the efficacy of this combination has been proved in a RCT enrolling naive patients, for whom it can be considered a recommended alternative regimen. All togheter these data give an optional recommendation level [CII]. Current evidences for effectiveness of DTG+3TC and DTG+RPV are based on few patients.
The results of the two SWORD studies, have been recently announced (Llibre et al., 2017). However, since the publication of the Italian Guidelines is dated November 22th, 2016, these data were not included in the present work.

Boosted protease inhibitors (PI) monotherapy
(*Table 5*).
Improvement of toxicity profile together with reduction of treatment costs are the main advantages supporting the switch to boosted-PI monotherapy in suppressed patients. 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 indicated 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%).
It should be noted that the only RCT evaluating ATV/r monotherapy (MODAT) was interrupted due to virological inferiority at 48 weeks compared to triple therapy. Similarly, the prolonged 96 weeks 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

Table 5 - *Summary of rationale and advantage/disadvantages of monotherapy for treatment optimization.*

Class of optimization	*Aims*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*Referencese*
From dual or triple therapy to DRV/r o DRV/c 800/100 mg QD	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	Cameron *et al.,* 2008; Arribas *et al.,* 2009; Bierman *et al.,* 2009; Pulido *et al.,* 2009; Gutmann *et al.,* 2010; Cahn *et al.,* 2011b; Arribas *et al.,* 2012; Valantin *et al.,* 2012; Arribas *et al.,* 2014a; d'Arminio Monforte *et al.* 2014; Gianotti *et al.,* 2014; Pinnetti *et al.,* 2014; Paton *et al.,* 2015 Antinori *et al.,* 2015; Pinnetti *et al.,* 2014; Geretti *et al.,* 2016; Gianotti *et al., 2016*
From dual or triple therapy to ATV/r o ATV/c 300/100 mg QD	Reduce/ Prevent NRTI associated toxicity.	Reduced virological efficacy, especially in patients HIV/HCV co-infected and in patients with HIV-1 RNA >100000 cp/ ml before starting cART; contraindicated in HBsAg positive patients.	[CI] in patients experiencing toxicity induced by NRTIs or not reccomended as a preventive measure	Spagnuolo *et al.,* 2014; Swindells *et al.,* 2006; Karlström *et al.,* 2007

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 <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 nadir CD4 T cell count above 200 cells/μl to select HIV-1 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. In the MONOI and MONET studies, other additional factors able to predict virological failure of DRV/r monotherapy were identified, such as HIV-1 viremia based on a ul-

Table 6 - *Summary of rationale and advantage/disadvantages regimens with reduced doses/administration (including FDC and STR).*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*References*
From NVP + 2 NRTI and from EFV + 2 NRTI to TDF/FTC/ RPV (a)	Improvement of adherence or toxicity reduction	Lower metabolic impact and improvement of EFV associated neurological symptoms.	Slight reduction of eGFR (uncertain clinical relevance).	[BII]	Mills *et al.,* 2013; Allavena *et al.,* 2014; Mora-Peris *et al.,* 2014; Gianotti *et al.,* 2015; Cazanave *et al*., 2015; Pinnetti *et al*., 2015
From NNRTI to EVG/COBI/ FTC/TAF (b) or EVG/COBI/ FTC/TDF (c)	Reducing toxicity.	Lower incidence of CNS adverse events; slight improvement of metabolic profile	Slight reduction of eGFR, but limited when using TAF (uncertain clinical relevance).	[AI]	Pozniak *et al.,* 2014; Mills *et al.,* 2015b; Mills *et al*., 2015c; Mills *et al.,* 2016 Pozniak *et al*., 2016;
From PI/r to RPV/TDF/FTC (d)	Reducing toxicity.	Lower incidence of gastrointestinal adverse effects; Lower metabolic impact	Lower genetic barrier.	[AI]	Palella *et al.,* 2014; Giannotti *et al.,* 2015;
From PI/r or PI/c to EVG/ COBI/FTC/TAF (c,e) or EVG/ COBI/FTC/TDF (f)	Reducing toxicity.	Increased virological success, improved patient satisfaction, minor adverse events. Proteinuria reduction and improvement in BMD.	Slight reduction of eGFR, but limited when using TAF (uncertain clinical relevance). Lower genetic barrier.	[AI]	Mills *et al*., 2016; Pozniak *et al*., 2016; Arribas *et al*., 2016
From all regimens to DTG/ABC/3TC (g)	Reducing toxicity	Increased patient satisfaction.	Cardiovascular toxicity derived from the use of ABC cannot be ruled out; increased number of adverse events.	[BI]	Fantauzzi *et al.,* 2015; Lake *et al*., 2016
From LPV/r to ATV/r or ATV/c. From LPV/r to DRV/r or ATV/r once daily	Reducing specific toxicity	Lower impact on lipid metabolism and gastrointestinal adverse effects. Reduced pill burden.	ATV increases the risk of hyperbilirubinemia.	[AII]	Gatell *et al.,* 2007; Mallolas *et al.,* 2009; Ucciferri *et al.,* 2013

a) Although RCTs are missing, observational studies showed a low risk of virological failure in virologically suppressed patients switching to RPV/FTC/ TDF STR

b) A randomized clinical trial including 434 patients the simplified regimen STR EVG/COBI/FTC/TDF was compared to standard NNRTI based antiretroviral regimens. At week 48, simplification arm showed virological non-inferiority (93% *vs* 88%), minor CNS disorders, and a tendency to an increase eGFR and a lower metabolic impact compared to the control group.

c) Switching to TAF based therapies limits kidney toxicity and can be considered as a therapeutic choice in patients experiencing renal insufficiency. Furthermore, TAF proved to have superior virological success (GS-109 Study).

d) In the SPIRIT study, 476 virologically suppressed HIV-1 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. At week 48, 89.3% of the simplified RPV group maintained viral suppression. Additional observational studies failed to identify significant risk of virological failure in patients with no history of previous resistance or risks of toxicity.

e) The GS-109 study (RCT including 601 patients from ATV/r + FTC/TDF to EVG/COBI/FTC/TAF FDC) 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.

f) One randomized clinical trial including 433 STR patients simplified to EVG/COBI/FTC/TDF showed superiority in virologic suppression at week 48 of the simplified group compared to the control group with PI based antiretroviral (94% *vs* 87%); moreover simplified patients had a significant improvement in quality of life and reduced, in particular, gastrointestinal adverse events.

g) One randomized clinical trial including 551 patients who switched to a simplified STR regimen DTG/ABC/3TC showed non-inferiority in virologic efficacy at week 48 of the simplified group compared to the control group with unchanged antiretroviral therapy. Although patients included in the simplification group showed an improvement in the degree of patient satisfaction, this study arm showed a greater number of adverse events leading to discontinuation of treatment.

trasensitive assay (HIV-RNA >1 copy/ml o >5 copies/ml) and HIV-1 DNA levels at baseline.
Increase in viral replication in cerebrospinal fluid (CSF) was sporadically reported among patients enrolled in MOST, MONOI and MONET studies, leading to the hypothesis of a possible association between PI/r monotherapy and an increasing risk HIV-1 replication in the CSF and of neurocognitive impairment. However, in the PROTEA trial, no case of developing HIV-1 viraemia in CSF was observed in patients with a CD4 T cell nadir >200 cell/µl. Moreover, the analysis of the tree RCTs (PIVOT, PROTEA and MODAT) 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.
In light of the above mentioned studies, switching to DRV/r monotherapy can be moderately recommended in presence of NRTI associated toxicity [BI]. Moreover, it 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, and a nadir T CD4 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-1 RNA [AIII] and proviral DNA [CIII], followed by resumption of triple therapy [AIII] are recommended.

Pill burden reduction (*Table 6*)
Different therapeutic approaches have been developed in order to reduce the regimen complexity and promote the adherence including once daily regimens, fixed dose combinations (FDC) and single tablet regimens (STR). 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.
Switching from PI to a different antiretroviral class (NNRTI 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

Table 7 - *Summary of rationale and advantages/disadvantages of other optimization strategies.*

Class of optimization	*Aims*	*Additional potential advantages*	*Potential disadvantages*	*Degree of recommendation/ Level of evidence*	*Literature*
From FTC/ TDF to FTC/ TAF	Prevention or reduction of specific toxicity.	Effective Maintenance of efficacy. Lower impact on renal toxicity. Lower impact on bone turn over.	Slight worsening of the lipid profile, whose clinical implications in the long term still pending	[AI]	Mills *et al.,* 2013; Pozniak *et al.,* 2015; Raffi *et al.,* 2016; Mills *et al.,* 2016;
From EFV/ FTC/TDF or RPV/FTC/ TDF to RPV/ FTC/TAF	Prevention or reduction of toxicity.	Proteinuria reduction. BMD improvement. Improvement of neuropsychiatric disorders when switching from EFV/FTC/TDF		[AI]	Orkin *et al.* 2016
From PI/r or PI/c to RAL (a)	Reduction of toxicity.	Lower gastrointestinal disorders; lower metabolic impact	Lower genetic barrier, non-inferiority not reached in a study, RAL BID regimen (at least until the approval of the RAL QD formulation), not recommended in case of previous failures to NRTIs. The strategy is eventually to be performed after at least 6 months of virologic suppression.	[BI]	Eron *et al.,* 2010; Martínez *et al.,* 2007; Curran *et al.,* 2012
From ATV/r to ATV (b)	Reduction of specific toxicity.	Hyperbilirubinemia Reduction. Modest reduction in lipids, fewer side effects.	Lower genetic barrier, not to be co-admistred with with TDF and anti-acids	[CII]	Ghosn *et al.,* 2010; Squires *et al.,* 2012

a) A randomized study that analyzed the switch from LPV/r to RAL in patients with virologic suppression did not reached the virological non-inferiority. The main cause of failure was the presence of previous virologic failures and therefore the likely resistance to NRTIs. A second randomized study instead demonstrated non-inferiority virological, presumably thanks to a longer period of previous virologic suppression before the switch, of at least 6 months. Both studies also demonstrated a favorable impact on blood lipids; furthermore, in the SPIRAL study the switch to RAL has significantly reduced the use of statins and increased bone density.
b) Indicated in patients with intolerance to ritonavir and contraindications to cobicistat. Not recommended in case of co-administration of tenofovir or anti-acid drugs. In this case, if it is necessary - for toxicity - ritonavir interruption, the ATV plasma concentration must be periodically verified through TDM.

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

Other optimization strategies
We refer the reader to *Table 7*.

The use of anti HCV drugs for the therapeutic management of HIV/HCV infected patients

Treatment with direct acting antivirals (DAAs) should be considered for all HIV-1 infected patients with chronic hepatitis virus infections.
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-1 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.

Pre-Exposure Prophylaxis

The pre-exposure prophylaxis (PrEP) with the combination of TDF/emtricitabine (FTC), in a continuous (daily) or intermittent ("on demand") is currently recommended as effective for the prevention of HIV-1 transmission [AI in people at high risk of acquiring HIV-1 infection- Efficacy was demonstrated in both controlled clinical studies and in their "open" extensions as well as in other observational studies. The studies, performed also in Europe, demonstrate that the effectiveness of the PrEP in preventing HIV-1 infection is strongly correlated with adherence to treatment, and adherence to PrEP protocol should be considered as a critical issue for PrEP success [BII] (Grant *et al*., 2010; Molina *et al*., 2015; McCormack *et al*., 2016; Hanscome *et al*., 2016; Funner *et al*., 2016; Spinner *et al*., 2016; Sagaon-Teyssier L *et al*., 2016). Based on available evidences (Centers for Disease Control and Prevention, 2014; World Health Organization, 2016), specific guidelines have been issued, and the European Commission on Recommendation of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted the extension of a business in the 28 European Union countries for FTC + TDF as PrEP (European Medicines Agency, 2016a; European Medicines Agency, 2016b).

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List of abbrevations
3TC: lamivudine; ABC: abacavir; ATV/r: ritonavir boosted atazanavir; ARV: antiretroviral drugs; BMD: bone mineral density; cART: combined antiretroviral therapy; COBI: cobicistat; CSF: cerebrospinal fluid; DTG: dolutegravir; DRV/r: ritonavir boosted darunavir; EFV: efavirenz; EVG: elvitegravir; FDC: fixed dose combinations; FTC: emitricitabine; GFR: glomerular filtration rate; 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; PI/r: ritonavir boosted protease inhibitor; RAL: raltegravir; RCT: randomized clinical trials; RPV: rilpivirine; RTV: ritonavir; STR: single tablet regimens; SVR: sustained virological response; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

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