

# Evidence-based renewal of the Italian guidelines for the use of antiretroviral agents and the diagnostic-clinical management of HIV-1 infected persons

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## SUMMARY

The Italian Society for Infectious and Tropical Diseases (SIMIT) in collaboration with the Technical Health Committee (Sections L and M) of the Italian Ministry of Health have supported the renewal of the 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 2017 version of the Italian Guidelines for the management of HIV-1 infected patients and the use of antiretroviral drugs. New recommendations were released framing the clinical questions the use of antiretrovirals according to the Patient Intervention Comparator Outcome (PICO) methodology and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Diagnostic tools for immunological and virological monitoring, when to start, what to start, optimization and therapeutic failure were updated in order to include the recommendation obtained with these newly developed methods. 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 2017 version of the Italian Guidelines for the management and the use of antiretroviral drugs (Antinori *et al.*, New Microbiol 2017) with the chapter related to HIV treatment notably revised in comparison to previous version. The implementation of a new method for drafting the guidelines was made necessary following the publication

of the Law No 24 of 8 March 2017 (<http://www.gazzettaufficiale.it/eli/id/2017/03/17/17G00041/sg>). The objective of this new regulation is the harmonization of the relationship between doctors and patients, through the approval of the new National System Guidelines. The law also suggests to align guidelines to internationally recognized standards; as a result, the new recommendations were released using the Population, Intervention, Comparison and Outcome (PICO) question format according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher *et al.*, 200). The new format was used to implement updated recommendations concerning the diagnostic tools for immunological and virological monitoring, when to start therapy, what to start, treatment optimization and therapeutic failure.

### Key words:

Antiretroviral therapy; HIV; Treatment guidelines.

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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. This version should not be considered completely exhaustive with respect to the full text version of the Guidelines. For a complete review of clinical and therapeutic relevant topics such as continuum of care, management of comorbidities, as well as populations (elderly, women, immigrants, children), conditions (drug and/or alcohol addiction, detention), and situations (transplants) requiring special attention we refer the reader to the extended version of the Guidelines. Similarly, while references cited herein refer only to the current update, a complete review of literature is available in the extended version of the Guidelines (HIV/AIDS Italian Expert Panel 2017).

## METHODOLOGY

Based on the PICO methodology, (Guyatt *et al.*, 2011) and the GRADE system, the HIV Guidelines Working Group decided to adopt a shared and univocal framing of clinical questions, specifying, for each question, the patient population, the intervention of interest, the comparator, and the outcomes of interest. The topics were selected based on the analysis of the scientific literature and the comparison with other Guidelines. Clinical needs and questions have been identified analysing the controversial areas, in which the identification of reference criteria and recom-

mendations, according to the principles of evidence-based medicine, are pivotal for the clinical decisions. The literature review was based on a search strategy for English-language articles in PubMed. Randomized controlled trials (RCTs), retrospective or prospective cohort studies with a control (concurrent or historical group) and the abstracts from the last two years International conferences were included. A modified frame from DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents was used to assess the strength of the recommendations (Table 1) (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents 2014). Ratings were discussed and approved by the entire Panel according to the usual rules.

## DIAGNOSTIC TOOLS FOR VIROLOGICAL AND IMMUNOLOGICAL MONITORING

### Virology

The burden of plasma HIV-RNA (viremia or viral load) is a surrogate marker that allows to predict the risk of clinical progression of the infection (prognostic marker) and evaluate the extent of the therapeutic response (Mellors *et al.*, 1996). Recent studies have highlighted a new unit of measurement, defined as “HIV-RNA copies produced per year” (HIV viremia copy-years), which corresponds to the area under the curve of longitudinal viremia values, and represents the cumulative amount of virus circulating in the organism within the indicated time frame. The achievement of permanently undetectable viremia is the goal of ART.

### Integrase genotypic resistance test

Given the widespread use of integrase inhibitors (INI) in clinical practice and the different genetic barrier of these drugs, the characterization of the integrase gene becomes particularly useful, not only at the time of failure, but also at the beginning of therapy with this class of drugs. In this regard, an increase in the prevalence of resistance to integrase inhibitors has been observed in recent years in patients treated with antiretroviral therapy (Lepik *et al.*, 2017). In addition, cases of transmission of strains resistant to these drugs begin to be reported (Menza *et al.*, 2017; Hurt *et al.*, 2011; Hernandez *et al.*, 2017). Finally, the high prevalence of polymorphisms potentially associated with INI resistance in newly diagnosed patients (Casadella *et al.*, 2017)

**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.

**Table 2** - Management of genotypic resistance test in treatment naïve patients.

VIROLOGY	
<i>Protease and reverse transcriptase</i>	
Q.1 Is there any advantage in performing a genotypic resistance test in all naïve patients?	R.1 genotypic resistance tests (GRT) in HIV-infected patients naïve is always recommended [AII]
Q.2 Is there any advantage to perform a genotypic resistance test in all patients with virological failure?	R.2 GRT in HIV infected patients with virological failure is always recommended [AII]
<i>Integrase</i>	
Q.3 Is there any benefit in assessing INI resistance test in HIV-infected patients naïve to therapy?	R.3 INI resistance test is recommended in naïve patients [BIII]
Q.4 Is there any benefit in assessing INI resistance in HIV-infected patients who start first-line regimens or other regimens containing INI?	R.4 INI resistance test is recommended in all patients starting an INI-based regimen [AIII]
Q.5 Is there any benefit in assessing INI resistance in HIV-infected patients who failed an INI regimen?	R.5 INI res.5 INI resistance test is always recommended in all HIV-infected patients who failed INI based regimen [AI]

References for the table above: Lepik *et al.* 2017; Menza *et al.* 2011; Hernandez *et al.* 2017; Casadella *et al.* 2015 Vandamme *et al.* 2011; Fernandez Caballero *et al.* 2016; Armenia *et al.* 2015; Katlama *et al.* 2016.

**Table 3** - Management of CD4+ in HIV-infected patients.

IMMUNOLOGY	
Q.1 Is the monitoring of the absolute number of CD4+ T cells associated with the percentage value of CD4+ T cells and the CD4/CD8 ratio a better indicator of immunological recovery than the monitoring of the CD4+ T cells count alone?	R.1 The absolute number of CD4+ T cells is currently the most validated prognostic immunological marker, as it is the strongest predictor of clinical progression (AIDS and non-AIDS events). It allows to determine the indication at the beginning or the suspension of the prophylaxis for opportunistic infections. [AI].
Q.2 In which clinical context the association of the above mentioned markers can provide a real advantage?	R.2 The percentage value of CD4+ T cells and the CD4/CD8 ratio should be evaluated in conjunction with the CD4+ T cell absolute count in order to obtain a better estimate of the immune system function, especially in patients with a risk of poor CD4+ T cell count recovery. (low CD4 + nadir, co-infections) [AII].
Q.3 It is believed that, in patients treated with ART and HIV-RNA <50 cp/μl and steady CD4+>500 cells/μl, monitoring frequency of CD4+T cell counts may be delayed and measured with intervals> 6 months [BII]	R.3 In ART treated patients with stable HIV-RNA <50 cp/μl and steady CD4 +>500 cells/μl, monitoring frequency of CD4 + counts may be delayed and measured with intervals> 6 months [BII]

References for the table above: Duro *et al.* 2017; Caniglia *et al.* 2017; Gale *et al.* 2013; Hyle *et al.* 2013; Gianotti *et al.* 2017.

indicates the usefulness of carrying out integrase resistance testing even in naïve patients in order to monitor the possible emergency of transmitted resistance to INI (Table 2).

### Immunology

The CD4+ T cell counts are the only validated immunological diagnostic marker in randomized controlled trials. Despite several non-randomized and cohort studies tried to identify additional immunological markers (e.g CD4/CD8 ratio), no other marker has been currently validated in the clinical management of HIV-1 infected patients. In subjects not treated with ART, CD4+T cell counts are reduced by about 4% per year. In response to therapy, a 50-100 cells/μL/year increase in the number of CD4+T cells is obtained (Kaufmann *et al.*, 2003). However, in a considerable proportion of subjects (about 25%), called immunological non-responders (INRs), this increase may be of a lower or variable extent (Gazzola *et al.*, 2009). Indicatively, a count CD4+T cells lower than 200 cells/μL as well as a percentage of CD4+T cells below 14% are associated with an increased risk of opportunistic infections (Table 3) (Ledergerber *et al.*, 2004; Gourlay *et al.*, 2012).

## CLINICAL GUIDELINES: ANTIRETROVIRAL THERAPY

### When to start

The decision when to start ART has to take in account multiple factors that concern both the health of the

HIV-infected patient, in the short and long term, and the role of ART in reducing the transmission of infection itself, also aiming at containing the epidemic (TasP, Treatment as Prevention). It is for these reasons that is strongly recommended to provide ART to all people infected with HIV [AI]. It is specified that, to avoid the transmission of HCV to the partner, this panel recommends, nevertheless, the use of condoms in case of anal intercourse in subjects with active HIV/HCV co-infection [AIII] (Table 4) (Foster A. *et al.*, 2016).

### Opportunistic infections

In the course of opportunistic infection (OI), although the beginning of ART is always recommended, it is preferable to respect some deadlines (Table 5).

### What to start?

#### First Line ART

The choice of a specific ART must be based on patients' individual needs.

The major advantage of the backbones comprising TDF, compared to the ones including ABC, lies in the fact that they do not require testing for the presence of HLA-B57 01 and that they have a greater antiviral activity and genetic barrier against HBV.

Furthermore, the initial (first 6 months) use of ABC has been correlated with increased risk of myocardial infarction in subjects with high cardio vascular risk (Sabin *et al.*, 2008; SMART/INSIGHT and the D:A:D Study Groups *et*

**Table 4** - When to start antiretroviral treatment.

WHEN TO START	
<i>Acute infection</i>	
Q.1 Is there any advantage in starting ART before the results of genotypic resistance tests for HIV and HLA-B5701 in HIV infected patients with an acute infection?	R.1 Immediate initiation of ART is recommended without waiting for the results [AII].
<i>Chronic infection</i>	
Q.1 Is there any benefit in starting ART in HIV-infected naïve patients with CD4 +>500 cells/μL compared to waiting to start when the CD4 + count is <500 cells/μL?	R.1 ART should be initiated in all subjects, regardless of the CD4+ cell count [AI] Rationale The studies indicate that ART is associated with a clinical benefit on progression to AIDS or even death in subjects with CD4+ >500 cells/μL lymphocytes; early beginning of ART is also associated with an improved of quality of life. A further benefit of early ART initiation is a reduction in transmission of HIV.

References for the table above: Ananworanich *et al.* 2016; Henrich *et al.* 2017; INSIGHT START Study Group 2015; Temprano ANRS 12136 Study Group. 2015; O'Connor *et al.* 2017; Achhra *et al.* 2017; Kunisaki *et al.* 2016; Lifson *et al.* 2017.

al., 2008). On the other hand, ABC, compared to TDF, offers the advantage of the possibility to be used in subjects with advanced renal insufficiency, without requiring dose adjustments (Table 6, 7, 8) (Sax et al., 2009; Sax et al., 2011; Daar et al., 2011; McComsey et al., 2011; Post et al., 2010;

Moyle et al., 2013; Smith et al., 2009; Fabbiani et al., 2014; Walmsley et al., 2013; Orrell et al., 2017; Walmsley et al., 2015; Wohl et al., 2016; Arribas et al., 2017; Gallant et al., 2017; Bedimo et al., 2016; Costarelli et al., 2016; Winston et al., 2017).

**Table 5** - When to start ART in a patient with an opportunistic infection.

Opportunistic Infections	
Q.1 Is there any benefit to starting immediately ART in HIV-infected naïve patients with <i>Pneumocystis jirovecii</i> pneumonia compared to waiting to start at the end of pneumonia treatment?	R.1 AIDS patients with <i>Pneumocystis jirovecii</i> must start ART within 2 weeks of diagnosis.
Q.2 Is there any benefit to starting immediately ART in HIV-infected naïve patients with pulmonary TB compared to waiting to start 15 days after starting TB therapy?	R.2 In AIDS patients with pulmonary TB ART should be started within 2 weeks from the start of TB therapy when CD4+ is <50 cell/mm <sup>3</sup> , and within 8 weeks from start anti-TB therapy in all co-infected HIV/TB patients [AI]
Q.3 Is there any benefit to starting immediately ART in AIDS patients with TB meningitis compared to waiting the end of antibiotic treatment for TB?	R.3 In AIDS patient with TB meningitis ART should be started at the end of induction phase of TB treatment [AI]
Q.4 Is there any benefit to starting immediately ART in AIDS patients with cryptococcal meningitis compared to waiting the end of antibiotic treatment?	R.4 In AIDS patients with cryptococcal meningitis, ART should be started at the end of induction therapy [AI]

References for the table above: Torok et al. 2011; Makadzange et al. 2010; Boulware et al. 2014; Bicanic et al. 2009.

**Table 6** - First line ART: the choice of backbones.

FIRST LINE ART	
Recommended regimen options	
Q.1 What are the best two nucleoside reverse transcriptase inhibitors (NRTIs) to start therapy in terms of efficacy and tolerability in naïve HIV-infected patients?	R.1 In naïve HIV-infected patients, it is recommended to initiate therapy with regimens containing a tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) [AI] or tenofovir alafenamide (TAF)/FTC [AI] or, limited to the combination with dolutegravir, abacavir (ABC)/lamivudine (3TC) [AI].

**Table 7** - First line ART: the choice of the third drug.

Options	
Q.1 What is the third favourite drug to start ART in terms of efficacy and tolerability in HIV-infected naïve patients?	R.1 A regimen based on integrase inhibitors (INSTI) [AI] is recommended for initiation of therapy in naïve patients, or, limited to patients with HIV-RNA <100,000 copies/mL and CD4+ >200 cells/μL, on RPV [AI]. Regimens based on boosted protease inhibitors are recommended only in conditions that do not favour adherence or starting treatment before the availability of the resistance test result is needed [AII]
Q.2 Does ART with at least three antiretroviral principles active in a single tablet (3D-STR) offer advantages in terms of efficacy, quality of life and adherence compared to therapeutic regimens with the same 3 active drugs, but with multiple tablets (3D-MTR) as initial therapy in HIV-infected naïve patient?	R.2 In the initial therapy an antiretroviral regimen with at least three active ingredients in a single tablet (STR) has advantages in terms of adherence [BII] (AII for regimens with NNRTI) and efficacy [BIII] (AIII for NNRTI regimens)
Q.3 Is the Dual Therapy (two different active antiretrovirals) an effective therapeutic option compared to ART with three active antiretroviral principles in HIV-infected naïve patients?	R.3 Dual therapy cannot be currently considered a therapeutic option similar to ART with three active drugs in terms of efficacy, and is therefore not recommended for the initiation of therapy in HIV-infected naïve patients [AI]
Q.4 Does the addition of a fourth drug to an ART regimen composed of at least three active antiretroviral principles, offers advantages in terms of therapeutic efficacy in HIV-infected naïve patients with chronic infection and with HIV-RNA >500,000 cp/mL?	R.4 The addition of a fourth drug does not offer documented benefits over an ART regimen with three active ingredients and is therefore not recommended for initiation of therapy in the chronically infected patient [AI].
Q.5 Does the addition of a fourth drug to an ART regimen composed of at least three active antiretroviral principles offer advantages in terms of therapeutic efficacy in treatment of HIV-infected naïve patients with acute infection?	R.5 During acute infection the addition of a fourth drug does not offer documented benefits compared to an ART with three active drugs [AI]

References to the above table: Orell et al. 2017; DeJesus et al. 2012; Eron et al., 2017; Molina et al. 2014; Cohen et al. 2014; Mills et al. 2015; Wohl et al. 2016; Astuti et al. 2014; Colombo et al. 2013; Engsig et al. 2014; Taneja et al. 2012; Fabbiani et al. 2016; Brunetta et al. 2015; Colombo et al. 2013; Homar et al. 2012; Rockstroh et al. 2013; Lennox et al. 2014; Cahn et al. 2017; Sax et al. 2012; DeJesus et al. 2012; Squires et al. 2016; Gallant et al. 2013; Gallant et al. 2015; Tashima et al. 2014; Mills et al. 2015; Eron et al. 2017; Cohen et al. 2013; Molina 2011; Cohen 2012; Cohen 2014; Cohen 2011; Nelson 2013; Sax et al. 2015; Molina et al. 2015; Daar et al. 2011; Kulkarni 2017; Rhee et al. 2015; Andreis et al. 2017; Slama et al. 2016; Dutertre et al. 2017; Stein et al. AIDS. 2015; Arkaiz et al. 2012; Crauwels et al. 2013; Raffi et al. 2014; Lambert-Niclot et al. 2016; Bernardino et al. 2015; Cahn et al. 2014; Stellbrink et al. 2016; Sued et al. 2017; Cahn et al. 2017; Taiwo et al. 2017; Crowell et al. 2016; Valcour, et al. 2015; Ostrowski et al. 2015; Chéret et al. 2015; Markowitz et al. 2014.

**Table 8 - Antiretroviral regimens recommended for starting ART.**

Regimen	Degree of recommendation/ Level of evidence
Recommended regimen options (for all conditions)	
TDF/FTC+RAL	[AI]
TAF/FTC+RAL	[AI]
TAF/FTC/EVG/COBI	[AI]
TDF/FTC+DTG	[AI]
TAF/FTC+DTG	[AI]
ABC/3TC+DTG or ABC/3TC/DTG	[AI]
TDF/FTC/RPV (for patients with HIV-RNA <100,000 copies/mL and T CD4+ count >200 cells/μl)	[AI]
TAF/FTC/RPV for patients with HIV-RNA <100.000 cp/mL and T CD4+ count >200 cells/μl)	[AII]
Recommended regimen options (for particular conditions)	
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, or for therapy initiation in pregnant patients)	[AII]
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]

References to the above table: Lennox *et al.* 2009; Raffi *et al.* 2013a; Raffi *et al.* 2013b; Rockstroh *et al.* 2013; Lennox *et al.* 2014; Sax *et al.* 2015; Clotet *et al.* 2014; Walmsley *et al.* 2013; Weller *et al.* 2014; Molina *et al.* 2011; Cohen *et al.* 2012; Cohen *et al.* 2013a; Cohen *et al.* 2014; 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; Clumeck *et al.* 2014; Lennox *et al.* 2014; Tashima *et al.* 2014; Gallant *et al.* 2015; Mills *et al.* 2015.

### Treatment optimization

The main aims of therapeutic optimization are: overcoming an ongoing toxicity (reactive switch); preventing predictable toxicity (preventive or proactive switch); promoting adherence by safely reducing the number of tablets or doses; addressing unfavourable drug interactions. The therapeutic schemes listed in *Table 9* represent the reference frame and every modification of the regimen must always consider the following priorities: maintaining virological suppression, and ensuring, with reasonable certainty, that the potential benefits for the patient outweigh

the potential risks (the switch must ultimately be an advantage for the individual patient) (*Table 9*).

### Therapeutic failure

The current availability of powerful and well tolerated antiretroviral drugs of various classes allows to set up long-lasting therapeutic regimens in the vast majority of patients. However, therapeutic failure due to the presence of a sub-optimal virological response (virological failure), unsatisfactory immunological response (immunological failure), as well as, to a lesser extent, clinical progression

**Table 9 - Antiretroviral regimens recommended for treatment optimization.**

Treatment optimization	
Q.1 In patients effectively treated with ART based on three active drugs in multiple tablets, does the switch to regimens that include ART with 3 drugs in a STR improve duration of the virological response, adherence and/or quality of life?	R.1 Switching to a STR improves adherence in observational studies; no randomized trials addressed this issue; however, some STR improves quality of life and patients satisfaction [BII]. In terms of virological response the switch to STR proved to be not inferior to the standard regimen.
Q.2 In patients treated with ART based on three active drugs, does the switch to a dual therapy maintain virological response, reduce toxicity and improve tolerability?	R.2 Virological suppression can be maintained with the switch to some regimens: 1. DTG+RPV [AI]; 2. ATV/r+3TC, DRV/r+3TC [AI for switches from boosted PIs, BI for switches from other regimens]; 3. DRV/r+RAL, DRV/r + RPV [CI]; 4. DTG+3TC [BII].
Q.3: In patients treated with ART based on three active drugs, does the switch to monotherapy with a boosted PI or DTG maintain the virological suppression, reduce toxicity and improve tolerability?	R.3 The switch study from three active drugs to one single drug demonstrated insufficient control of HIV replication. DRV/r mono therapy [CI]. DTG mono therapy must to be avoided [AI].
Q.4 In patients treated with PI-based or NNRTI-based ART with three active drugs, does the switch to an INSTI or to a RPV-based regimen maintain virological suppression, reduce toxicity, improve tolerability and modify drug-drug interactions?	R.4 The following switches from a boosted PI are recommended: RPV [AI]; EVG/COBI/FTC/TDF [AI]; DTG [AI]. Also the switch from NNRTIs to an INSTI or RPV is recommended [AI]. In contrast, the switch from a boosted PI to MVC is optional [CI], and the switch from a boosted PI to RAL is recommended with caution [BI].
Q.5 In patients treated with three active drugs including TDF/FTC, does the switch to ABC/3TC- or from TDF to TAF maintain the virological suppression, reduce toxicity, improve tolerability and modify drug-drug interactions?	R.5 Switch from TDF/FTC based regimen to ABC/3TC - or TAF/FTC based regimen maintain virological suppression and reduces renal and bone toxicity [AI]. Caution is recommended for patients at risk for cardiovascular events [AI].

References to the above table: Airoldi *et al.* 2010; Raffi *et al.* 2015; Sterrantino *et al.* 2012; Molina *et al.* 2015; Walmsley *et al.* 2015; Palella *et al.* 2014; Arribas *et al.* 2017; Trottier *et al.* 2017.

**Table 10** - Management of antiretroviral failure.

Therapeutic failure	
Q.1 Is the genotypic resistance tests (GRT) useful during ART in patients with low level viremia failure?	R.1 GRT is recommended in all patients before starting therapy and in all patients with virological failure [AI]. GRT in patients with low level viremia has proved to be reliable, also for the integrase enzyme [AII].
Q.2 Is the determination of the Therapeutic Drug Monitoring (TDM) for drugs used in patients in virological failure indicated in absence of resistance mutations?	R.2 The determination of the TDM for the drugs in use, even with the limitations inherent the execution and interpretation of the test, is a useful complement to the choice of the subsequent regimen and is therefore recommended [BII].
Q.3 Is the enhancement of ART with a fourth drug indicated in patients with frequent viral blip?	R.3 Intensification with a fourth drug in patients with frequent viral blip is not recommended [AII]
Q.4 Is simplification strategy advisable in patients with history of virological failure?	R.4 In these populations it is recommended a simplification with high genetic barrier drugs [BII]

References to the above table: Santoro *et al.* 2014; Armenia *et al.* 2015; Huhn *et al.* 2017.

(clinical failure) still occur in a non-negligible proportion of patients (Table 10).

### List of abbreviations

3TC: lamivudine; ABC: abacavir; ATV/r: ritonavir boosted atazanavir; ART: combined antiretroviral therapy; COBI: cobicistat; DTG: dolutegravir; DRV/r: ritonavir boosted darunavir; EVG: elvitegravir; FDC: fixed dose combinations; FTC: emtricitabine; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; RAL: raltegravir; RPV: rilpivirine; RTV: ritonavir; STR: single tablet regimens; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

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