

## Special Article



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\*The Committee for Clinical Guidelines for the Diagnosis and Treatment of HIV/AIDS of the Korean Society for AIDS

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# The 2018 Clinical Guidelines for the Diagnosis and Treatment of HIV/AIDS in HIV-Infected Koreans

The Korean Society for AIDS

## ABSTRACT

Since the establishment of the Committee for Clinical Guidelines for the Diagnosis and Treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) by the Korean Society for AIDS in 2010, clinical guidelines have been prepared in 2011, 2013, and 2015. As new research findings on the epidemiology, diagnosis, and treatment of AIDS have been published in and outside of Korea along with the development and introduction of new antiretroviral medications, a need has arisen to revise the clinical guidelines by analyzing such new data. The clinical guidelines address the initial evaluation of patients diagnosed with HIV/AIDS, follow-up tests, appropriate timing of medication, appropriate antiretroviral medications, treatment strategies for patients who have concurrent infections with hepatitis B or C virus, and treatment in pregnant women. Through these clinical guidelines, the Korean Society for AIDS and the Committee for Clinical Guidelines for the Diagnosis and Treatment of HIV/AIDS would like to contribute to overcoming AIDS by delivering the latest data and treatment strategies to healthcare professionals who treat AIDS in the clinic.

**Keywords:** Human immunodeficiency virus; Diagnosis; Anti-retroviral agents; Guideline

## 1. WHAT'S NEW IN THE GUIDELINES?

The following key changes have been made to update the 2015 guidelines

1. Tenofovir alafenamide/emtricitabine (TAF/FTC) is newly entered as a preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone.
2. Dolutegravir (DTG) is newly entered as a preferred integrase strand transfer inhibitor (INSTI). However, DTG should be avoided for women with child bearing potential and during first 12 weeks of their pregnancy.
3. Efavirenz (EFV) is no longer a preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) and reclassified as an alternative drug.
4. Darunavir/cocistat (DRV/c) is newly entered as a preferred protease inhibitor (PI).
5. Atazanavir/ritonavir (ATV/r) and lopinavir/ritonavir (LPV/r) are no longer preferred PIs and reclassified as alternative drugs.

\*The following recommendation is a practical guideline based on the current (Oct. 2018) domestic Korean status, on the diagnosis and treatment of HIV infected patients. Rather than applying the following principle to the general, we recommended that patient treatment be based upon clinical decision making, according to the diversity of every individual patient.

\*The following recommendation can be used for educational and personal clinical practices, but it cannot be utilized for any commercial or clinical evaluation purposes. Those who wish to use the following guideline for any other purposes must admit a written form and must get written consent from the committee.

#### Conflict of Interest

No conflicts of interest.

6. For the patient on a suppressive regimen whose CD4+ T cell count has consistently maintained, CD4+ T cell monitoring interval can be extended to every 6 months. Continued CD4+ T cell monitoring for virologically suppressed patients whose CD4+ T cell counts have been consistently >500 cells/mm<sup>3</sup> for at least 2 years may be considered optional.
7. Rilpivirine (RPV) is introduced as a preferred NNRTI.
8. Elvitegravir (EVG)/cobicistat (COBI) is introduced as a preferred INSTI. It is available only as a single co-formulated tablet as tenofovir/emtricitabine/elvitegravir/cobicistat.
9. Didanosine (ddl)/lamivudine (3TC), which were advocated as an alternative NRTI backbone, are no longer recommended.
10. Sections on antiretroviral use in pregnant women have been added.
11. An updated human immunodeficiency virus (HIV)/hepatitis C virus (HCV) treatment guideline with direct-acting antiviral (DAA) therapy has been added.
12. EFV can be used as an alternative in pregnant women who wish to take medications once daily.

## 2. INITIAL EVALUATION AND FOLLOW-UP TESTS

When an HIV-infected individual visits a medical institution for the first time, a sufficient review of the patient's symptoms, underlying diseases, financial status, high-risk behaviors, and psychological factors should be conducted, and a baseline evaluation including laboratory tests should also be performed. If active treatment and counseling can be offered based on these results, they will contribute to the patient's better understanding and adaptation to their disease [1-4].

A CD4+ T cell count should be performed and percentage calculated. A CD4+ T cell count is needed to determine the stage of AIDS and the need for highly active antiretroviral therapy (HAART) and prophylaxis for opportunistic infections by evaluating the risks of complications due to HIV infection [5, 6]. A plasma HIV titer is required to evaluate the prognosis and determine the need for HAART [7-9]. According to previous studies, 30–40% of individuals with progressed HIV infections show anemia, leukopenia, or thrombocytopenia, and 75% show abnormalities in hepatic or renal function [10]. Therefore, a complete blood count (CBC), liver function tests, fasting glucose level, and fasting lipid profile are required upon initial presentation [11]. Calcium, phosphate, and alkaline phosphatase should be measured at intervals of 24–48 weeks if the following risk factors are present: old age, female sex, hypogonadism, history of fracture, family history of hip fracture, vitamin D deficiency, smoking, decreased physical activity, and history of steroid use. Bone densitometry should be conducted at 2-year intervals to evaluate bone diseases in men over the age of 50, perimenopausal women, and individuals with a history of fracture, a high risk of falls, a history of steroid use, or hypogonadism [4]. To diagnose latent tuberculosis, a tuberculin skin test (TST) or interferon (IFN)- $\gamma$  release assay (IGRA) should be performed. In individuals with progressed HIV infections, even if the TST is negative, repeat tests are recommended once the CD4+ T cell count recovers to at least 400/mm<sup>3</sup> [4]. As TST is influenced by decreased cellular immunity in patients with AIDS, chest radiography is required regardless of the TST results if patients present with respiratory symptoms; moreover, sputum acid-fast bacilli staining and a tuberculosis culture should be conducted [12]. Serologic tests for hepatitis A virus, hepatitis B virus (HBV), and HCV and screening tests for syphilis, toxoplasmosis, gonorrhea and other sexually transmitted diseases should be performed [13-17].

The HLA-B\*5701 test should be conducted before administration of abacavir. When the HLA-B\*5701 test is not possible, the risk of a hypersensitivity reaction and other precautions should be explained in sufficient detail to the patient before prescribing [18-20]. A genotypic resistance test is recommended in patients with AIDS who are undergoing their first HAART or in patients who are considering a change in medication owing to virologic failure [21-24]. A pregnancy test should be conducted in premenopausal women who are considering the use of EFV [25, 26].

A CD4+ T cell count and plasma HIV RNA titer should be repeated every 12-16 weeks to evaluate treatment responses. If patients respond well to antiretroviral treatment, thus showing continued virologic suppression for 2 years or longer and are clinically stable, follow-up tests can be conducted every 24 weeks. In individuals with progressed HIV infection, follow-up testing for opportunistic infections should be continued for the first 12 months of treatment [27-29]. If tests for syphilis, TST, *Toxoplasma gondii*, cytomegalovirus antibody, and hepatitis (A, B, and C) are negative upon initial presentation, they should be repeated at intervals of 48 weeks.

### 3. INDICATIONS FOR HAART

Because antiretroviral treatment can decrease HIV-related disease morbidity rate and mortality in all HIV-infected individuals regardless of CD4+ T cell count, it is recommended in all individuals. Moreover, as antiretroviral treatment is also an effective way to decrease the risks of transmission of HIV, it is recommended in all HIV-infected individuals for preventive purposes.

Randomized control studies conducted on patients with a CD4+ T cell count below 200/mm<sup>3</sup> and a history of AIDS-defining diseases reported that HAART improves patient survival and delays the progression of AIDS [30-32]. Moreover, multiple observational cohort studies with long-term follow-up reported that initiating HAART in patients with a CD4+ T cell count above 200/mm<sup>3</sup> was more effective with respect to clinical outcomes than starting it in patients who already have an immune deficiency with a CD4+ T cell count below 200/mm<sup>3</sup> [33, 34].

The Strategic Management of Antiretroviral Therapy (SMART) study was a multinational clinical trial conducted in 5,400 patients with a CD4+ T cell count above 350/mm<sup>3</sup>, and the participants were randomly assigned to a group that received continued HAART and another group that stopped HAART until their CD4+ T cell count decreased below 250/mm<sup>3</sup>. In additional analysis conducted on 249 patients who were not undergoing HAART at the time of registration, the group that started HAART immediately had decreased risks of serious AIDS-related diseases and non-AIDS-related diseases compared with the group that delayed the start of HAART until their CD4+ T cell count decreased below 250/mm<sup>3</sup> ( $P = 0.06$ ) [35].

The Strategic Timing of Antiretroviral Therapy (START) study, which was a multinational clinical trial conducted on asymptomatic HIV-infected individuals with a CD4+ T cell count above 500/mm<sup>3</sup>, compared the occurrence of AIDS, non-AIDS-related complications, and mortality between an early treatment group that started HAART immediately and a delayed treatment group that started HAART only after their CD4+ T cell count decreased below 350/mm<sup>3</sup> or clinical indications had occurred [34]. The incidence of serious AIDS-related and non-AIDS-related complications was 0.60/100 person-years in the early treatment group and

1.38/100 person-years in the delayed treatment group; in other words, the risks of serious AIDS- and non-AIDS-related complications were significantly lower in the early treatment group than in the delayed treatment group. In the START study, the benefits of early treatment were observed consistently regardless of sex, age, viral titer, and national economic status. Early treatment led to noticeable decreases in the risks of AIDS, tuberculosis, and cancer as well as serious non-AIDS-related complications.

HAART is helpful not only for the treatment of HIV infection but also for prevention. The HIV Prevention Trials Network (HPTN) 052 study published in 2011 evaluated whether early HAART in HIV-infected persons is helpful in preventing the transmission of HIV in HIV-infected/non-HIV-infected couples. A total of 1,793 HIV-infected/non-HIV-infected couples registered for the study and were divided into a group undergoing immediate HAART and another group undergoing delayed treatment after the CD4+ T cell count decreased below 250/mm<sup>3</sup>, in order to prospectively evaluate HIV transmission from infected individuals to non-infected individuals. The risk of HIV transmission was 95% lower in the group undergoing early treatment with a high CD4+ T cell count than in the group undergoing delayed treatment with a lower CD4+ T cell count [36]. The HPTN 052 study proved that early treatment of HIV-infected individuals benefits the patients and is effective from a public health point of view in preventing HIV transmission. Therefore, based on these findings, guidelines recommending early treatment in all HIV-infected individuals regardless of their CD4+ T cell count have been prepared.

These findings suggest that starting HAART regardless of CD4+ T cell count decreases the risks of diseases related to HIV infection or death and that it can also prevent the transmission of HIV in society as it can lower transmission risks. Based on these findings, it is recommended to start HAART in all HIV-infected individuals regardless of CD4+ T cell count.

## 4. INITIAL COMBINATION REGIMENS FOR THE ANTIRETROVIRAL-NAÏVE PATIENT

The panel recommends one of the following antiretroviral regimens in treatment-naïve patients: Two NRTIs + one INSTI, two NRTIs + one NNRTI, or two NRTIs + one protease inhibitor/ritonavir (PI/r) or protease inhibitor/cobicistat (PI/c). TAF/FTC, tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) are preferred NRTI backbones [37-39]. Zidovudine/lamivudine (ZDV/3TC) may be used when the preferred NRTI backbones are not suitable [40, 41]. DTG, raltegravir (RAL) and elvitegravir/cobicistat (EVG/c) can be used as a preferred INSTI [37, 42-49]. EVG/c is available only as a single co-formulated tablet as either tenofovir alafenamide fumarate/emtricitabine/elvitegravir/cobicistat or tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat. DTG should be avoided for women with child bearing potential and during first 12 weeks of their pregnancy [50, 51]. RPV is a preferred NNRTI only if HIV RNA <100,000 copies/mL and CD4+ T cell count >200 cells/mm<sup>3</sup> [52, 53]. EFV is an alternative NNRTI when the preferred NNRTI cannot be used [54]. Darunavir/ritonavir (DRV/r) or DRV/c is a preferred drug when PI/r or PI/c is used [55]. ATV/r or atazanavir/cobicistat (ATV/c), atazanavir (ATV), and LPV/r are alternative drugs when the preferred PI/r or PI/c cannot be used [54, 56, 57]. But, unboosted ATV cannot be prescribed with TDF.

## 5. MANAGEMENT OF THE TREATMENT-EXPERIENCED PATIENT

Regular monitoring of plasma HIV-1 RNA is recommended to evaluate virologic response in treatment-experienced patients [58]. When virologic failure (HIV-1 RNA level >200 copies/mL) is detected, a drug-resistance test should be done while the patient is taking the failing antiretroviral regimen. Even if continued low-grade viremia (HIV-1 RNA level >50–200 copies/mL) is seen, it is not necessary to view this as failure of virologic suppression or to change medications [59]. The goal of treatment for patients with virologic failure is to re-establish virologic suppression (HIV-1 RNA level <50 copies/mL). The patient's treatment history and past and current resistance test results should be used to identify at least two, preferably three, fully active agents for patients with virologic failure. It is not recommended to add only one effective antiretroviral agent for patients with virologic failure. Discontinuing or holding antiretroviral agents in patients in virologic failure should be avoided as this may lead to decreases in the CD4+ T cell count. If maximal viral suppression is not possible due to the limitations of active agents, antiretroviral therapy should be continued to avoid clinical deterioration [60].

## 6. PREVENTION, MANAGEMENT, AND TREATMENT OF CHRONIC HEPATITIS B AND C COINFECTION IN HIV-INFECTED PATIENTS

All HIV-infected patients should be tested for HBV and HCV infection, and assessed for immunity to hepatitis A. If patients are non-immune, vaccination is recommended. Hepatitis B surface antigen (HBsAg) positive patients should be tested for HBV-DNA quantitatively before the initiation of HAART. Regardless of CD4+ T cell count or HBV treatment status, HAART-including agents with both anti-HIV and anti-HBV activities are recommended. As the NRTI backbone of HAART, a combination of TDF or TAF/FTC or lamivudine (3TC) is recommended [61-63]. If HBV treatment is needed and TDF cannot be used, the alternative option is entecavir in addition to a fully suppressive HAART [64]. Monotherapy with entecavir is not recommended [65]. Monotherapy with peg interferon- $\alpha$  may be used in some patients. However, monotherapy with adefovir, combined therapy with 3TC or FTC, or use of telbivudine is not recommended. When medications with anti-HBV effects (*e.g.*, 3TC and entecavir) are discontinued, HBV reactivation may lead to serious hepatocellular damage. Therefore, patients should be discouraged from discontinuing the medications on their own, and clinical aspects should be closely monitored through frequent liver function tests when HBV treatment is discontinued [66]. When antiretroviral agents need to be changed owing to failed HIV therapy, the agent used for HBV treatment should be continued and other antiretroviral agents should be used for HIV suppression if plasma HBV is under good control. Initial testing for HCV should be performed by measuring anti-HCV in the blood, and if positive, a confirmatory test measuring the plasma HCV-RNA level should be done quantitatively. In patients with HIV/HCV coinfection, pre-treatment assessments prior to HCV treatment including the HCV genotype, liver fibrosis, stage of liver disease should be performed. HAART should be considered for HIV/HCV co-infected patients regardless of CD4+ T cell count [67-69]. If the CD4+ T cell count is low at <200/mm<sup>3</sup>, antiretroviral therapy should be initiated immediately, and HCV treatment can be delayed until HIV treatment stabilizes. Identical combinations of medications can be used for HAART-naïve patients with HIV/HCV coinfection or HIV infection. However, when treatment of both HIV

and HCV infection is required, drug interaction and toxicity should be considered. Direct-acting antiviral (DAA) therapy without IFN should be considered first, and DAA with known interaction with antiretroviral agents should be used. Because DAAs may interact with various medications, caution is required regarding its interaction with antiretroviral agents. When an anti-HCV agent does not include IFN, HBV may be reactivated in HBV/HCV/HIV co-infected patients. Therefore, HCV/HIV-infected patients with active HBV infection (HBs Ag positive) should be first treated with antiretroviral therapy with two or more anti-HBV medications.

## 7. MANAGEMENT OF HIV-INFECTED PREGNANT WOMEN

Physicians treating premenopausal HIV-infected women should provide counseling on family planning and contraception to decrease the risk of unwanted pregnancy and the possibility of transmission to the fetus. All HIV-infected patients considering pregnancy should receive HAART, and pregnancy should be achieved only after HIV RNA is suppressed maximally under the detection limit. Initiation of HAART before 28 weeks of pregnancy has reduced the rate of perinatal transmission of HIV from approximately 30% to 0.1-0.5% [70, 71]. Thus, early HAART is recommended for all pregnant HIV-infected women regardless of their clinical, virologic, or immunologic state. When selecting an antiretroviral regimen for a pregnant woman, clinicians should consider various factors, such as influence on the fetus, pharmacokinetics during pregnancy, clinical experience in pregnant women, comorbidities, drug interactions, drug resistance and compliance.

Among NRTIs, ABC/3TC and TDF/FTC co-formulations are recommended for treatment-naïve pregnant women, and ZDV/3TC may be considered as an alternative. No NNRTIs are recommended as a preferred agent for treatment-naïve HIV-infected pregnant women. However, although previous guidelines recommended avoiding EFV before 8 weeks of pregnancy owing to risks of fetal deformity, EFV can now be used as an alternative in pregnant women who wish to take medications once daily based on the recent study findings [72-74]. In particular, HIV-infected pregnant women in their first trimester, if they achieved sufficient virologic suppression before pregnancy, may continue EFV-based combination therapy. Unnecessary changes in medication may lead to virologic failure and increase the risks of transmission to the fetus during pregnancy [75]. In addition, RPV may be used for treatment-naïve HIV-infected patients (CD4 T cell count >200 cells/mm<sup>3</sup>, HIV RNA titer <100,000 copies/mL). Among PIs, ATV/r and DRV/r are recommended for treatment-naïve HIV-infected pregnant women, and LPV/r may be used as an alternative. In case of INSTIs, RAL is recommended for treatment-naïve pregnant women based on safety and pharmacokinetic data.

## SUPPLEMENTARY MATERIAL

Guideline Korean version.

Supplementary material can be found with this article on-line <https://icjournal.org/src/sm/ic-51-77-s001.pdf>.

### Supplementary

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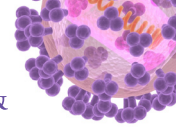
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