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Special Article

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Summary of 2021 Clinical Guidelines for the Diagnosis and Treatment of HIV/AIDS in HIV-infected Koreans

The Korean Society for AIDS

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Corresponding Author:
The Committee for Clinical Guidelines for the Diagnosis and Treatment of HIV/AIDS of the Korean Society for AIDS
The Korean Society for AIDS, 806, SeochoTown Trapalace, 23 Seocho-daero 74-gil, Seocho-gu, Seoul 06621, Korea.
Tel: +82-2-3487-1755
Fax: +82-2-585-8384
E-mail: kosa@kosaids.or.kr

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

Chairman
Jun Yong Choi (Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea)

Member of the Committee
Seong-Heon Wie (Division of Infectious Diseases, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea), Nam Joong Kim (Division of Infectious Diseases, Seoul

ABSTRACT

Since the establishment of the Committee for Clinical Guidelines for the Diagnosis and Treatment of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) by the Korean Society for AIDS in 2010, clinical guidelines have been prepared in 2011, 2013, 2015, and 2018. 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, recommendations for resistance testing, treatment for patients with HIV and tuberculosis coinfections, 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 contributes to overcoming AIDS by delivering latest data and treatment strategies to healthcare professionals who treat AIDS in the clinic.

Keywords: HIV/AIDS; Diagnosis; Antiretroviral treatment; Guidelines

PURPOSE

The purpose of these guidelines is to revise the recommendations for clinical guidelines for the diagnosis and treatment of human immunodeficiency virus (HIV)-infected patients in Korea, which was announced in 2018 by the Korean Society for AIDS, to reflect the current situation [1]. It became necessary to revise the recommendations following the introduction of several new antiretroviral drugs in Korea and the publication of many new research results regarding the HIV.

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National University Hospital, Seoul, Korea), Ji Hwan Bang (Division of Infectious Diseases, Seoul National University-Seoul Metropolitan Government Boramae Medical Center, Seoul, Korea), Joon Young Song (Division of Infectious Diseases, Korea University College of Medicine, Seoul, Korea), So Youn Shin (Division of Infectious Diseases, College of Medicine, Catholic Kwandong University, Incheon, Korea), Jae Phil Choi (Division of Infectious Diseases, Seoul Medical Center, Seoul, Korea), Bum Sik Chin (Center for Infectious Diseases, National Medical Center, Seoul, Korea)

*These recommendations present the basic principles for the diagnosis and treatment of HIV infection in persons infected with human immunodeficiency virus that reflect the domestic situation in June 2021. Rather than generally applying these treatment guidelines for all patients, it should simply be used as a reference, as it is important for the clinician to make the final decision considering the various clinical situation of each patient.

Conflict of Interest
No conflicts of interest.

SCOPE

Considering the domestic situation as of June 2021, these treatment guidelines present recommendations on: Initial laboratory assessment, follow-up tests and frequency necessary for diagnosis and treatment of HIV-infected persons, eligibility to start antiretroviral treatment, selection of antiretroviral agents for those with or without treatment experience, treatment of patients with both HIV and hepatitis B/C virus infections, antiretroviral treatment of those also infected with tuberculosis, implementation and use of resistance tests, and antiretroviral treatment in pregnant women.

COMPOSITION OF THE COMMITTEE FOR CLINICAL GUIDELINES FOR THE DIAGNOSIS AND TREATMENT

In June 2020, the Committee for Clinical Guidelines for the Diagnosis and Treatment was organized by the Korean Society for AIDS, which was tasked to revise the clinical guidelines for the diagnosis and treatment of HIV-infected persons.

PROCESS FOR ARRIVING AT KEY QUESTIONS

To prepare the clinical guidelines for the diagnosis and treatment of HIV infection in Korea, contents were divided into the following categories: initial assessment and follow-up tests, eligibility for starting highly active antiretroviral therapy (HAART), HAART in treatment-naïve patients, HAART in previously treated patients, antiretroviral treatment for patients infected with both HIV/hepatitis B virus (HIV/HBV) or HIV/hepatitis C virus (HIV/HCV), antiretroviral treatment for patients infected with both tuberculosis/HIV, implementation and use of resistance tests, and HAART in pregnant women. Key questions were selected after reviewing relevant literature, foreign guidelines, as well as tests and antiretroviral treatment drugs currently available in Korea in consideration of various situations that may be encountered in actual clinical practice. In addition, the Committee held several meetings to arrive at the final key questions for the clinical guidelines for each field.

STRENGTH OF RECOMMENDATION AND QUALITY OF EVIDENCE FOR RECOMMENDATION

The strength of recommendation and the quality of evidence for recommendation used in these guidelines adopted the method used in the latest guidelines from the US Department of Health and Human Services. Strength of recommendation was classified into 3 (A, B, C) as in **Table 1**, and the quality of evidence for recommendation was presented as I, II and III (**Table 1**).

Table 1. Strength of recommendation and quality of evidence for recommendation

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

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1) Strength of Recommendation

(1) A ~ Strong recommendation for the statement
(2) B ~ Moderate recommendation for the statement
(3) C ~ Optional recommendation for the statement

2) Quality of Evidence for Recommendation

(1) I ~ One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
(2) II ~ One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
(3) III ~ Expert opinion

Patients who have not received HAART were labeled as treatment-naive patients, whereas those who have received HAART in the past were labeled as treatment-experienced patients.

The acronyms used in these clinical guidelines are as follows:
ABC, abacavir; ATV, atazanavir; ATV/c, atazanavir/cobicistat; ATV/r, ritonavir-boosted ataznavir; BIC, bictegravir; DRV, darunavir; DRV/c, darunavir/cobicistat; DRV/r, ritonavir-boosted darunavir darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; EVG/c, elvitegravir/cobicistat; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; LPV/r, ritonavir-boosted lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; ZDV, zidovudine; 3TC, lamivudine.

RECOMMENDATION

1) Initial assessment and follow-up test

*(1) What are the laboratory tests to be conducted at the initial visit for an HIV-infected person? (***Table 2***)*

Table 2. Initial assessment in HIV-infected persons

HIV antibody test
CD4+ T cell count and percent
Complete blood count and differentials
Basic chemistry, liver and renal function tests
Fasting glucose, lipid profile
Serologic tests for hepatitis A, B and C viruses
Syphilis serology
Screening tests for other sexually transmitted diseases
Chest X-ray
Tuberculin skin test or IFN-γ release assay
Toxoplasmosis serology
Bone densitometry

HIV, human immunodeficiency virus; IFN, interferon.

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1. Conduct CD4+ T cell count and percentage, as well as plasma HIV RNA viral load (A-I). In HIV-infected persons with opportunistic infections requiring treatment, the CD4+ T cell count and plasma HIV viral load tests are repeated once they have stabilized after acute treatment (A-II) [2-4].
2. Conduct a complete blood count (CBC) and a general chemistry test, including differential count (A-III) [2, 4, 5].
3. Conduct serological screening for hepatitis B (A-III), hepatitis C (A-III), and hepatitis A (B-III) [2, 4].
4. Screen for opportunistic infections such as toxoplasmosis (B-III) [6].
5. To screen for tuberculosis, conduct a tuberculin skin test (TST) or an Interferon (IFN)-γ release assay (A-II). In persons with advanced HIV infection, re-testing is recommended once CD4+ T cell count is recovered to at least 200 count/mm^3 even if the result of TST is negative (A-III) [6].
6. In women, conduct a Papanicolaou smear test to screen for cervical cancer [7].
7. Perform screening for other sexually transmitted diseases such as syphilis (A-II), gonorrhea, and chlamydia (B-II) [4, 6, 8].
8. At the initial visit, a HIV genotypic resistance test should be performed to evaluate transmitted resistance (A-II) [2, 4].

(2) Which imaging studies should be performed at the initial visit of an HIV-infected person?

1. Perform chest radiography to screen for tuberculosis (A-III) [4, 6].
2. Bone mineral density test should be considered for men over 50 years of age, postmenopausal women, as well as those with a history of fractures, steroid use, or hypogonadism (B-III) [2, 4].

(3) Which laboratory tests should be checked prior to initiating HAART?

1. Before initiating HAART, the number of CD4+ T cell count should be measured (A-II), and HIV viral loads should be checked within 4 weeks before starting antiretroviral therapy (A-III) [2, 4].
2. Conduct a pregnancy test if there is a possibility of pregnancy in women before initiating HAART [2].
3. Consider conducting an HLA-B*5701 test before prescribing abacavir (A-I). If test is not feasible, prescribe it after fully explaining the possibility of hypersensitivity reactions and precautions to the patient (C-III) [2, 4].
4. Genotypic resistance testing is recommended for HIV infected persons who are starting HAART for the first time, or for patients who are considering a change of treatment regimen due to virologic treatment failure (A-II) [2, 4].

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(4) How frequent should laboratory tests be performed to check for disease progression and drug toxicity in HIV-infected people taking antiretroviral drugs?

1. In principle, CD4+ T cell count should be repeated every 12 - 24 weeks in patients receiving HAART (B-II), but it can be performed every 48 weeks if there is no change in the patient's condition upon recovery of immune function following the administration of antiretroviral treatment (B-II) [2, 9].
2. In patients undergoing HAART, quantitation of plasma HIV RNA should be repeated every 12 - 16 weeks (A-III). The follow-up interval can be increased to every 24 weeks if viral suppression has been continuously observed for 2 years or more, and is clinically stable (A-III) [2, 10].
3. In patients undergoing HAART, CBC and general chemistry tests are repeated at intervals of 12 - 16 weeks, and if they show continuous virus suppression for 2 years or more and are clinically stable, the tests can be performed at intervals of 24 weeks (A-III) [11].
4. In the case of administering HAART containing zidovidine, a CBC test and white blood cell percentage as follow-up tests are performed 2 - 8 weeks after starting the treatment.
5. General chemistry and liver function tests are performed 2 - 8 weeks after the start of antiretroviral treatment, and follow-up tests are performed every 12 - 24 weeks thereafter. A fasting triglyceride test is repeated every 24 weeks if abnormal and every 48 weeks if normal, while a fasting blood glucose test is repeated every 12 - 24 weeks if abnormal and every 48 weeks if normal [2, 4, 12].
6. Assessment of opportunistic infections is required prior to the initial visit and HAART. Although the risk of opportunistic infection gradually decreases after HAART is started, intensive follow-up to screen for opportunistic infections is required for the first 12 months of treatment in individuals with advanced HIV infection (B-II) [6, 13].
7. Serological tests for viral hepatitis and opportunistic infections should be followed up every 48 weeks if the result at initial visit was negative (A-III) [6, 13].

2) Eligibility for starting HAART

(1) Who are eligible to start HAART and when?

1. HAART is recommended to reduce mortality and morbidity in all HIV-infected individuals regardless of CD4+ T cell count (A-I) [14-18].
2. For all HIV-infected persons, HAART is recommended to prevent transmission of HIV infection from HIV-infected persons to others (A-I) [19].
3. It is recommended to start HAART on the day of diagnosis of HIV infection or as early as possible after diagnosis of HIV infection (A-II) [20, 21].
4. Initiation of HAART may be delayed in HIV-infected persons with tuberculous meningitis or cryptococcal meningitis (B-I) [22, 23].

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3) Antiretroviral treatment in treatment-naïve patients

(1) Which combination of antiretroviral drugs is preferred for treatment-naïve patients? **(Table 3)**

1. Combinations with INSTI

Antiretroviral combination including INSTI is recommended for most treatment-naïve patients. The specifics are as follows:

(1) ABC/3TC/DTG (A-I) [24-26]

ABC can induce a fatal hypersensitivity reaction, which is associated with HLA-B*5701.

ABC/3TC combination is not appropriate for patients who also have HBV infection.

There is concern that ABC may lead to cardiovascular complications.

DTG is known to increase the frequency of neural tube defects in fetuses. Therefore, when administering drugs containing DTG to pregnant women within 12 weeks of pregnancy, administration of the drug is decided only after discussing the benefits and

Table 3. Recommended antiretroviral regimens for naïve HIV-infected patients

Regimen	Requirements
Recommended regimens	
ABC[a,b]/3TC/DTG[c,d]	HLA-B*5701 negative, HBs Ag negative
TAF[d]/FTC/BIC[d]	
TAF[d](or TDF[e])/FTC + DTG[c,d]	
TAF[d](or TDF[e])/FTC + RAL	
3TC/DTG[c,d]	HBs Ag negative, HIV RNA <500,000 copies/mL
TAF[d,f](or TDF[e])/FTC + DRV/c(or DRV/r[b])	Use if regimens including an INSTI are not appropriate, Should be taken with food
Alternative regimens	
TAF[d,f](or TDF[e])/FTC/EVG/c	Should be taken with food
ABC[a,b]/3TC + RAL	HBs Ag negative
TAF[d,f](or TDF[e])/FTC + ATV/c(or ATV/r)	Should be taken with food
ABC[a,b]/3TC + DRV/c(or DRV/r[b])	HBs Ag negative, Should be taken with food
ABC[a,b]/3TC + ATV/c(or ATV/r)	HBs Ag negative, Should be taken with food
TAF[d,f](or TDF[e])/FTC + EFV	
TAF[d,f](or TDF[e])/FTC + RPV	HIV RNA <100,000 copies/mL & CD4 >200 cells/μL, Should be taken with food
ABC[a,b]/3TC + EFV	HBs Ag negative, HIV RNA <100,000 copies/mL
Other regimens	
2NRTI[f] backbone (including ZDV/3C) + a PI such as unboosted ATV or LPV/r[b]	Unboosted ATV cannot be used with TDF, Unboosted or boosted ATV should be taken with food

[a]ABC might cause fatal hypersensitivity reactions.
[b]ABC, DRV/r, and LPV/r could increase cardiovascular risk.
[c]DTG might cause neural tube defects in infants. Thus, discuss with your patients the drug's benefits and harms before prescribing DTG, especially if your patients are in the first 12 weeks of pregnancy.
[d]TAF, DTG, and BIC are associated with weight gain.
[e]TDF could cause renal and bone toxicity.
[f]Use 10 mg (not 25 mg) of TAF if used with EVG/c or PI.
HIV, human immunodeficiency virus; ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir; HLA, *human leukocyte antigen; HBs Ag, hepatitis B virus surface antigen;* TAF, tenofovir alafenamide; FTC, emtricitabine; BIC, bictegravir; TDF, tenofovir disoproxil fumarate; RAL, raltegravir; RNA, ribonucleic acid; DRV/c, darunavir/cobicistat; DRV/r, ritonavir-boosted darunavir; INSTI, integrase strand transfer inhibitor; EVG/c, elvitegravir/cobicistat; ATV/c, atazanavir/cobicistat; ATV/r, ATV/r, atazanavir/ritonavir; EFV, efavirenz; RPV, rilpivirine; CD4, CD4+ T cell counts; ZDV, zidovudine; LPV/r, ritonavir-boosted lopinavir.

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risks with the patient.

DTG may result in weight gain.

(2) TAF/FTC/BIC (A-I) [27, 28]

Therapy including TAF/FTC can suppress both HIV and HBV in patients who also have HBV infection.

Both TAF and BIC may result in weight gain.

(3) TAF(or TDF)/FTC + DTG (A-I) [27]

Therapy including TAF(or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

Both TAF and DTG may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

DTG is known to increase the frequency of neural tube defects in fetuses. Therefore, when administering drugs containing DTG to pregnant women within 12 weeks of pregnancy, administration of the drug is decided only after discussing the benefits and risks with the patient.

(4) TAF(or TDF)/FTC + RAL (A-II for TAF, A-I for TDF) [29, 30]

Therapy including TAF(or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

When administered in the above combination, TAF/FTC should be administered in a formulation containing 25 mg of TAF.

RAL should be taken as one 400 mg tablet twice a day, or two 600 mg tablets once a day.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and decreased renal function.

(5) 3TC/DTG (A-I) [31]

It is considered when HIV RNA <500,000 copies/mL.

It is not recommended for patients who also have HBV infection.

It is recommended that administration only be done after checking for the presence of HIV drug-resistant mutations.

DTG is known to increase the frequency of neural tube defects in fetuses. Therefore, when administering drugs containing DTG to pregnant women within 12 weeks of pregnancy, administration of the drug is decided only after discussing the benefits and risks with the patient.

DTG may result in weight gain.

2. Combinations with PI

If the combination of antiretroviral drugs containing INSTI is not appropriate, antiretroviral drugs containing DRV/c (or DRV/r) may be considered. The specifics are as follows:

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(1) TAF (or TDF)/FTC + DRV/c(or DRV/r) (A-I) [32, 33]

Therapy including TAF (or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

When administered in the above combination, TAF/FTC should be administered in a formulation containing 10 mg of TAF.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

DRV/r can lead to cardiovascular complications.

DRV/c (or DRV/r) should be taken with meals.

*(2) Which combinations can be considered when it is difficult to use the recommended first-line antiretroviral combination that is for treatment-naïve patients? (***Table 3***)*

1. Combinations with INSTI

(1) TAF (or TDF)/FTC/EVG/c (B-I) [34, 35]

Therapy including TAF (or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

EVG/c is not recommended for pregnant women because it can induce a decrease in blood drug concentration during middle and late stages of pregnancy.

It should be taken with meals.

(2) ABC/3TC + RAL (B-II) [25]

ABC can induce a fatal hypersensitivity reaction, which is associated with HLA-B*5701.

The above drug combination is not appropriate for patients who also have HBV infection.

There is concern that ABC may lead to cardiovascular complications.

2. Combinations with PI

(1) TAF (or TDF)/FTC + ATV/c(or ATV/r) (B-I) [36, 37]

Therapy including TAF (or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

When administered in the above combination, TAF/FTC should be administered in a formulation containing 10 mg of TAF.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

ATV/c (or ATV/r) should be taken with meals.

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(2) ABC/3TC + DRV/c (or DRV/r) (B-II) [38]

ABC can induce a fatal hypersensitivity reaction, which is associated with HLA-B*5701.

The above drug combination is not appropriate for patients who also have HBV infection.

There is concern that ABC may lead to cardiovascular complications.

DRV/r can lead to cardiovascular complications.

DRV/c (or DRV/r) should be taken with meals.

(3) ABC/3TC + ATV/c (or ATV/r) (B-III for ATV/c and B-I for ATV/r) [39]

ABC can induce a fatal hypersensitivity reaction, which is associated with HLA-B*5701.

The above drug combination is not appropriate for patients who also have HBV infection.

There is concern that ABC may lead to cardiovascular complications.

ARV/c (or ATV/r) should be taken with meals.

3. Combinations with NNRTI

(1) TAF (or TDF)/FTC + EFV (B-II for TAF, B-I for TDF) [39]

Therapy including TAF (or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

(2) TAF (or TDF)/FTC + RPV (B-III for TAF, B-I for TDF) [40]

It is considered when HIV RNA <100,000 copies/mL and CD4+ T cell count >200 cells/μL.

Therapy including TAF (or TDF)/FTC can suppress both HIV and HBV in patients who also have HBV infection.

TAF may result in weight gain.

TDF may cause decreased bone mineral density and renal function.

RPV should be taken with meals.

(3) ABC/3TC + EFV (B-I) [39]

It is considered when HIV RNA <100,000 copies/mL.

ABC can induce a fatal hypersensitivity reaction, which is associated with HLA-B*5701.

The above drug combination is not appropriate for patients who also have HBV infection.

There is concern that ABC may lead to cardiovascular complications.

(3) Which drug combinations can be considered if the above-mentioned drug combinations are difficult to administer, or if the patient wishes to continue medications without side effects for a long time?

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1. Generally, treatment is administered in the form of an 2NRTI backbone + 3rd agent. ZDV/3TC can be considered as an 2NRTI backbone (C-I) that can be used in addition to ABC/3TC and TDF (or TAF)/FTC mentioned above (C-I). Meanwhile, as a 3rd agent, unboosted ATV (with food) and LPV/r can be considered in addition to the PI mentioned above (C-I).

2. If unboosted ATV is administered together with TDF, the concentration of ATV may decrease due to drug interaction; thus, administration of unboosted ATV with TDF should be avoided (B-II). Very little data are available regarding possible drug interactions with the co-administration of unboosted ATV and TAF. Therefore, it should be used only when absolutely necessary, and after consulting an expert in pharmacokinetics (C-II).

3. When administering LPV/r, TAF/FTC should be given in a formulation containing 10 mg of TAF (B-II).

4) HAART in treatment-experienced patients

(1) What should be done if low-grade viremia is found during antiretroviral treatment?

1. It is desirable to keep the plasma HIV RNA titer below 50 copies/mL after 24 weeks of antiretroviral administration. Low-grade viremia is defined as 50 - 200 copies/mL of viremia during antiretroviral therapy.

2. Approach to patients with a low degree of viremia

(1) Review drug compliance.

(2) Measure the HIV RNA titer again after 1 to 2 months.

(3) If it is difficult to obtain genotype resistance test results, consider a new drug combination based on previous antiretroviral treatment history (A-III).

(2) How should patients who have had virologic failure during antiretroviral therapy be treated?

1. Definition of virologic failure

Virologic failure is defined as a condition in which the HIV RNA titer exceeds 200 copies/mL after 24 weeks of antiretroviral administration.

2. Approach for patients with virologic failure

(1) Review the therapeutic effect of antiretroviral drugs.

(2) Review drug compliance, drug side effects, drug-drug interactions, and possible inhibition of absorption due to food intake.

(3) Conduct a drug resistance test. If possible, drug resistance testing is performed when antiretroviral drugs are being taken or within 4 weeks of discontinuation, and when the HIV RNA titer exceeds 1,000 copies/mL (A-I) [41].

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(4) If possible, conduct a drug concentration test (Therapeutic drug monitoring).

(5) Change the antiretroviral drug as soon as possible. The goal of a drug change is to reduce and maintain the HIV RNA titer to less than 50 copies/mL again within 6 months of instituting the change.

3. New combination of antiretroviral agents

(1) Adding at least two or more agents, or if possible, three effective antiretroviral agents to the treatment of patients who have reached viral treatment failure is recommended (A-I) [42, 43]. It is desirable to include a protease inhibitor that maintains sensitivity based on a drug resistance test and an antiretroviral agent of a class that has not been used before.

(2) It is not recommended to add only one effective antiretroviral agent to patients with virologic failure (B-I).

(3) In patients with virologic failure, discontinuation or temporary cessation of antiretroviral drugs should be avoided, as it may increase the viral titer and decrease the CD4+ T cell count (A-I) [44, 45].

(4) As much as possible, is recommended to maintain administration of antiretroviral drugs with minimal side effects to prevent a decrease in CD4+ T cell count, and to prevent clinical deterioration even in patients who have failed to suppress the virus or when it is impossible to suppress the virus (A-I) [46].

(3) How should patients in which the virus is suppressed during antiretroviral treatment, but the CD4+ T cell count response is low, be treated?

1. In general, the CD4+ T cell count increases gradually after administration of antiretroviral drugs. However, if viremia is not observed and the CD4+ T cell count is maintained at a low count (*e.g.*, <200/mm^3) for a long period of time, the incidence of infectious diseases, cardiovascular diseases, malignant tumors, and liver diseases increases.

2. Approach for patients with low CD4+ T cell count responses

(1) It is not recommended to add antiretroviral agents to patients who does not exhibit viremia (A-I) [47].

(2) It is not recommended to change antiretroviral drugs for the purpose of increasing the CD4+ T cell count in patients without viremia (B-III).

(3) It is not recommended to administer interleukin-2 for the purpose of increasing the CD4+ T cell count in patients without viremia (A-I) [48].

5) Antiretroviral treatment in patients with both HIV/HBV or HIV/HCV infections

(1) When should pre-treatment assessment and treatment for patients with both HIV/HBV infections be done?

1. Before starting antiretroviral therapy, all HBs Ag-positive HIV-infected persons should be quantitatively evaluated for HBV DNA (A-III).

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2. Regardless of the CD4+ T cell counts, it is recommended that all patients infected with both HIV/HBV be treated with a combination of antiretroviral agents that can treat both HIV and HBV (A-II).

(2) Which treatment should be selected in patients with both HIV/HBV infections?

1. FTC, 3TC, TDF and TAF have therapeutic effect on both HIV and HBV. Therefore, when selecting an antiretroviral agent in patients with both HIV/HBV infections, an NRTI combination which combines 3TC or FTC with TAF or TDF, is preferentially considered (A-I) [49-51].

2. If HBV treatment is required but TDF or TAF cannot be used, HAART and entecavir may be used to treat both HBV and HIV as an alternative therapy (B-I). Entecavir has a weak anti-HIV effect and causes M184V gene mutation when used alone without HAART; thus, it is not recommended to use entecavir alone without HAART (A-II) [52].

3. In some patients, peginterferon-α monotherapy may be used in combination (C-II).

4. Administration of adefovir or telbivudine is not recommended (C-II).

5. When a drug with an anti-HBV effect (*e.g.*, 3TC, entecavir) needs to be discontinued: If a drug with an anti-HBV effect is discontinued, recommendations should be given so that the patient does not voluntarily stop taking the drug, because this may lead to serious hepatocellular damage due to HBV reactivation. If HBV treatment is discontinued, frequent liver function tests should be performed and clinical features should be observed (A-II) [53].

6. When antiretroviral drugs need to be replaced due to HIV treatment failure and blood HBV virus titers are well-controlled, maintain the drugs used for HBV treatment and use other antiretroviral agents to induce blood HIV suppression (A-III).

(3) When should pre-treatment assessment and start treatment for patients with both HIV/HCV infections be done?

1. HCV screening should be performed on all HIV-infected persons and repeated annually (A-III).

2. Consider antiretroviral therapy for all patients infected with both HIV/HCV regardless of CD4+ T cell count (A-I) [54, 55].

3. HCV treatment should be considered for all patients infected with both HIV/HCV. Before antiviral treatment, the following evaluations are performed (A-I).

(1) HCV genotyping: An HCV RNA quantitative test and HCV genotyping, as well as gene subtype (Ia/Ib) testing, are performed before antiviral treatment (A-I).

(2) Assessment of the severity of liver disease: A liver biopsy can be performed to determine the timing of antiviral initiation and prognosis (B-I). Alternatively, a non-invasive liver fibrosis test can be done (B-I).

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(4) Which treatment should be given to patients with both HIV/HCV infections?

1. In patients with both HIV/HCV infections who have never been treated with HAART, the combination of antiretrovirals for initial treatment is the same as in HIV mono-infected patients (A-III).
2. Treat patients with both HIV/HCV infections similarly as those with HCV infection alone. Prefer instituting direct-acting antiviral (DAA) therapy that does not contain interferon. Use DAA with known interactions with antiretrovirals (B-I).
3. As DAA may cause drug interactions with various medications, be wary that this may lead to interactions with antiretrovirals (A-I).
4. When treating concurrent HBV/HCV/HIV infections, HBV may be reactivated if HCV is treated with DAA. For HCV/HIV-infected patients with active HBV infection (HBsAg-positive), treatment with antiretroviral regimens containing two or more anti-HBV agents (*e.g.*, a combination of TDF or TAF and FTC or 3TC) prior to initiation of HCV treatment should be given (A-III) [56, 57].

6) Antiretroviral treatment in patients with HIV/tuberculosis coinfection

(1) Who can receive antiretroviral treatment in patients with HIV/tuberculosis coinfection?

1. Patients infected with HIV/tuberculosis are eligible for antiretroviral therapy regardless of the patient's CD4+ T cell count (A-I).

(2) Does the time of initiation of antiretroviral treatment differ depending on the immune status of the patient infected with HIV/tuberculosis?

1. If tuberculosis develops in a patient who has been receiving antiretroviral treatment, start appropriate tuberculosis treatment immediately, but select the regimen and dose of antiretroviral treatment with caution due to drug interaction with rifamycin (A-II).
2. The timing of HAART initiation according to the CD4+ T cell count in HIV-infected persons with tuberculosis who were not receiving antiretroviral treatment is as follows:

(1) CD4+ T cell count <50 cells/mm^3: Start antiretroviral therapy as soon as possible within 2 weeks of starting tuberculosis treatment (A-I) [58-60].

(2) CD4+ T cell count ≥50 cells/mm^3: Start antiretroviral treatment within 8 weeks of starting tuberculosis treatment (A-I) [61].

(3) For pregnant women, regardless of the number of CD4+ T cell count, antiretroviral therapy should be started as soon as possible to prevent HIV transmission to the fetus, along with tuberculosis treatment (A-III).

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*(3) What are the considerations regarding drug interactions when treating HIV/tuberculosis coinfection? (***Table 4***)*

1. Rifampin is a key drug in the treatment of tuberculosis, but it is a potent inducer of CYP450, P-glycoprotein, and uridine diphosphate glucuronosyl-transferase 1A1. Because it interacts with TAF, INSTI, and PI, drug interactions should be considered when selecting and changing drugs (A-III).
2. TAF, BIC, EVG/c, PI, and RPV should not be used with rifampin (A-III).
3. When using rifampin, it is possible to use efavirenz 600 mg, and when using INSTI, it is necessary to increase the dose to DTG 50 mg BID and RAL 800 mg BID (A-II).

Table 4. Drug interactions between rifamycin and antiretrovirals

Rafamycin	Antretroviral agents	Effect on antiretroviral agents and/or concomitant antimycobacterial medication	Dosing recommendations and clinical comments
Rifampin	All PI	↓ PI concentration by >75%	**Contraindicated.** Consider rifabutin if a rifamycin is indicated.
	BIC	BIC AUC ↓ 75%	**Contraindicated.**
	EVG/c	Significant ↓ EVG and cobicistat expected	**Contraindicated.**
	DTG	Rifampin with DTG 50 mg twice daily (Compared to DTG 50 mg twice daily alone):	Patients without suspected or documented INSTI-resistance mutations:
		DTG AUC ↓ 54% and C_{min} ↓ 72%	Use DTG 50 mg twice daily suspected or documented INSTI-resistance mutations: Consider an alternative to rifampin, such as rifabutin
		Rifampin with DTG 50 mg twice daily (Compared to DTG 50 mg daily alone):	
		DTG AUC ↑ 33% and C_{min} ↑ 22%	
	RAL	RAL 400 mg: RAL AUC ↓ 40% and C_{min} ↓ 61%	Use RAL 800 mg twice daily instead of 400 mg twice daily.
		Rifampin with RAL 800 mg twice daily (Compared to RAL 400 mg twice daily alone):	
		RAL AUC ↑ 27% and C_{min} ↓ 53%	Do not coadminister RAL 1,200 mg once daily with rifampin.
	TAF	TAF is a P-glycoprotein substrate, its plasma concentrations may be reduced by rifamycin.	**Do not coadminister unless benefits outweigh risks.**
		TAF with rifampin (Compared with TAF Alone):	
		TAF AUC ↓ 55%	Intracellular TFV-DP levels are higher when TAF is co-administered with rifampin compared to when TDF is administered alone, but clinical outcomes have not been studied. If co-administered, monitor virologic response.
		TFV-DP AUC ↓ 36%	
	RPV	RPV AUC ↓ 80%	**Contraindicated.**
	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg daily and monitor for virologic response.
Rifabutin	DRV/r	Compared with rifabutin (300 mg once daily) Alone, Rifabutin (150 mg every other day) plus DRV/r: ↔ rifabutin AUC and metabolite AUC ↑ 881%	Recommended dose is rifabutin 150 mg once daily. Monitor for antimycobacterial activity and consider therapeutic drug monitoring.
	PI/c	↑ rifabutin expected	**Do not coadminister.**
		↓ cobicistat expected	
	BIC	Rifabutin 300 mg once daily:	**Do not coadminister.**
		BIC AUC ↓ 38% and C_{min} ↓ 56%	
	DTG	Rifabutin 300 mg once daily:	No dose adjustment needed.
		↔ DTG AUC and C_{min} ↓ 30%	
	EVG/c	Rifabutin 150 mg every other day with EVG/c once daily (Compared to Rifabutin 300 mg once daily alone):	**Do not coadminister.**
		↔ rifabutin AUC	
		25-O-desacetyl-rifabutin AUC ↑ 625%	
		EVG AUC ↓ 21% and C_{min} ↓ 67%	
	RAL	RAL AUC ↑ 19% and C_{min} ↓ 20%	No dose adjustment needed.

AUC, area under the curve; EVG/c, elvitegravir/cobicistat; DTG, dolutegravir; C_{min}, minimum concentration; INSTI, integrase strand transfer inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TFV-DP, tenofovir-diphosphate; RPV, rilpivirine; EFV, efavirenz; DRV/r, ritonavir-boosted darunavir; PI/c, protease inhibitor/cobicistat; BIC, bictegravir; darunavir/ritonavir.

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(4) When should antiretroviral therapy be started in HIV-infected persons with tuberculous meningitis?

1. When antiretroviral drugs are administered early for tuberculous meningitis, the frequency of adverse drug reactions is high; thus, intensive follow-up is required (A-I).
2. If intensive monitoring of drug interactions and central nervous system events can be achieved, it is recommended that treatment be started within 2 - 8 weeks, and if CD4+ T cell count <50 cells/mm^3, start treatment within 2 weeks (B-III) [22].

(5) Should antiretroviral therapy be discontinued if immune reconstitution inflammatory syndrome (IRIS) develops?

1. IRIS can appear in the form of unmasking IRIS, which occurs within a few weeks after initiation of antiretroviral treatment, as well as paradoxical IRIS within 3 months in 8% to 40% of patients infected with HIV/tuberculosis.
2. In patients infected with HIV/tuberculosis who develop IRIS, antiretroviral treatment and anti-tuberculosis treatment should be continued without interruption (A-III).
3. If IRIS occurs in a patient infected with HIV/tuberculosis, symptomatic therapy may be used. If symptoms are severe, corticosteroids may be given (A-II).

7) Implementation and use of HIV resistance testing

(1) What kinds of HIV resistance tests can be performed in Korea?

1. A genotypic resistance test is performed when therapeutic response to the initial treatment regimen is insufficient or virologic failure occurs (A-II). In patients who have an extensive treatment history or those who are at risk of developing a combination of complex resistance mutations that cannot be predicted by existing data, the predictive power of the genotypic resistance test may decrease. In such cases, a phenotypic resistance test is preferred, but this test is not readily offered in Korea.

(2) Should a resistance test be performed for patients who are treatment naïve in Korea?

1. HIV resistance test is recommended in patients who have never been treated with antiretroviral therapy to guide treatment decisions (A-II) [62-65].
2. If antiretroviral treatment is delayed, repeat testing may be considered at the time of treatment initiation (CIII) [66].
3. The initiation of treatment should not be delayed while waiting for the resistance test results in patients with acute or recent HIV infection, pregnant women with HIV, and in patients starting antiretroviral treatment immediately after HIV diagnosis. Treatment regimen can be modified when the resistance test result is available (A-III).
4. A genotypic resistance test is preferred over a phenotypic resistance test for determining regimen in treatment naive patients (A-III).

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(3) What are the cautions for performing a resistance test in treatment-experienced patients and in those who failed treatment?

1. It is performed when the virus is insufficiently suppressed despite taking antiretroviral drugs (A-II).
2. It is performed in case of virological failure, that is, when the plasma viral load is 1,000 copies/mL or more (A-I) [41].
3. If possible, the test should be performed while taking the drug. If it is stopped, the test should be conducted within 4 weeks (A-II) [67-69].
4. Resistance test at a plasma viral load of 500 - 1,000 copies/mL is also clinically useful (B-II). However, whether to perform the resistance test or not is up to the policy of testing institution. If it is less than 500 copies/mL, it is not recommended to conduct a resistance test because the test result is not reliable.
5. Resistance testing may still provide useful information to guide therapy while more than 4 weeks have elapsed since the treatment discontinuation; however, it is important to recognize that previously selected resistance mutations can be missed due to disappearance of drug-selective pressure (C-III).

(4) What precautions should be taken when interpreting resistance test results?

Because most current drug-resistance tests may not be able to detect previously acquired resistance mutations, prior test results should be used when designing a new regimen (A-III). In patients with extensive treatment histories, the predictive power of genotypic resistance tests may be poor.

8) Antiretroviral treatment in pregnant women

(1) How should HIV-infected patients be managed before pregnancy?

1. All HIV-infected women should receive antiretroviral treatments to restore their health and reduce sexual transmission (A-I) [14, 16].
2. Physicians treating HIV-infected female patients of childbearing age should provide counseling on family planning and contraception to reduce the possibility of unintended pregnancy and transmission of the virus to the fetus (A-I) [70-72].
3. All HIV-infected persons contemplating pregnancy should receive HAART and become pregnant only after HIV RNA has been maximally suppressed to undetectable levels (A-I) [73, 74].

(2) How should antiretroviral treatment be administered during pregnancy and before delivery?

1. All HIV-infected pregnant women are recommended to receive HAART as soon as possible regardless of clinical, virologic, or immunological status (A-I) [75-79].

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2. HIV-infected pregnant women should be given an opportunity to receive a full explanation about the benefits of antiretroviral treatment and the risks of each drug during pregnancy (A-III).

3. Because antiretroviral treatment has great benefits for the health of pregnant women and suppression of transmission to the fetus, treatment should not be stopped or postponed, but should be maintained throughout pregnancy (A-I) [78, 79].

4. A resistance test should be performed before starting antiretroviral treatment, and the start of treatment should not be delayed while awaiting the resistance test results (A-II) [80, 81].

5. Pregnant women whose HIV RNA titers increased to 500 - 1,000 copies/mL or more during antiretroviral therapy should be tested for resistance before any drug change is done (A-III).

*(3) What type of antiretroviral therapy is recommended for HIV-infected pregnant women? (**Table 5**)*

1. When selecting the drugs to be used for HAART, it is necessary to consider various factors aside from their effects on the fetus, including their pharmacokinetics in relation to pregnancy, clinical experience in pregnant women, concomitant diseases, drug interactions, drug resistance, and compliance (A-III). Refer to **Table 5** for details on drug selection.

(4) Which method of delivery should an HIV-infected pregnant woman undergo?

1. Pregnant women with a high HIV RNA titer exceeding 1,000 copies/mL in a quantitative HIV RNA test performed at 34 - 36 weeks of pregnancy should plan a cesarean section at 38 weeks of pregnancy, regardless of whether they are taking antiretrovirals or not, in order to minimize the possibility of transmission of the disease to the fetus (A-II) [82]. Pregnant women with HIV RNA titers of 1,000 copies/mL or less can follow general standard delivery guidelines.

2. Pregnant women whose HIV RNA titers after 34 - 36 weeks of pregnancy (or within 4 - 6 weeks of delivery) are unknown should plan in advance for cesarean delivery (A-II) [83, 84].

Table 5. Antiretroviral recommendations in treatment-naive HIV-infected women

Classes	Preferred agents	Alternative agents	Comments
NRTI	Abacavir/lamivudine, TDF/emtricitabine, TDF/lamivudine	Zidovudine/lamivudine TAF/emtricitabine	· Although data are limited, TAF plasma concentrations in pregnant women are similar to those seen in non-pregnant adults.
NNRTI	-	Efavirenz	· Although birth defects have been reported in animal studies of efavirenz, there has been no evidence of an increased risk for efavirenz-related birth defects in human pregnancy.
		Rilpivirine	· Etravirine is not recommended because of limited information regarding its use in pregnant women.
PI	Atazanavir/ritonavir, Darunavir/ritonavir	-	· Lopinavir/ritonavir is not recommended except in special circumstances, since it may increase the risk of preterm delivery and cause significant nausea compared to preferred/alternative agents. · Cobicistat-boosted PI agents are not recommended except in special circumstances, because of potential low drug levels and the occurrence of viral rebound in the second and third trimesters.
ITSTI	Raltegravir, Dolutegravir	-	· Elvitegravir/cobicistat is not recommended because of limited information regarding its use and inadequate levels of elvitegravir and cobicistat in the second and third trimesters.

HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide;-NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor.

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(5) How should antiretroviral treatment be administered during delivery?

1. Pregnant women whose HIV RNA titers are unknown or greater than 1,000 copies/mL should be administered intravenous zidovudine at the time of delivery (A-II) [85].

2. For pregnant women with an HIV RNA titer of less than 1,000 copies/mL after 34 - 36 weeks of pregnancy (or within 4 - 6 weeks of delivery) who are taking antiretrovirals, decide whether to administer antiretrovirals intravenously during delivery by considering both viral loads and adherence with antiretroviral treatments. Pregnant women who have high adherence to antiretroviral treatment and whose viral loads are fully suppressed to less than 50 copies/mL can forgo intravenous zidovudine administration during delivery, but they should continue oral antiretroviral treatment before and after delivery (B-II) [85, 86]. Pregnant women with an HIV RNA titer of 50 - 1,000 copies/mL should decide whether to administer zidovudine intravenously during delivery in consideration of adherence with antiretroviral treatment (C-II) [85, 87].

(6) What should be done post-delivery?

1. All HIV-infected pregnant women, regardless of whether they are receiving antiretroviral treatments, should avoid breastfeeding due to risk of transmission to the newborn (A-II) [88].

2. All newborns born to HIV-infected pregnant women, regardless of whether prophylactic antiretrovirals are administered to the mother before or after childbirth, should receive antiretroviral prophylaxis (A-I) [89, 90].

3. Antiretroviral therapy for newborns should be started as soon as possible within 6 hours after delivery (A-II) [89, 90].

SUPPLEMENTARY MATERIAL

Guideline Korean version.

Supplementary material can be found with this article on-line https://icjournal.org/src/sm/ic-53-592-s001.pdf.

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