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Chinese guidelines for the diagnosis and treatment of human immunodeficiency virus infection/acquired immunodeficiency syndrome (2024 edition)

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Abstract

The Acquired Immunodeficiency Syndrome Professional Group of the Society of Infectious Diseases of the Chinese Medical Association formulated the first edition of the *Chinese Guidelines for the Diagnosis and Treatment of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS)* (referred to as the Guidelines) in 2005. The 2024 edition of the Guidelines has been compiled by updating the 2021 fifth edition, incorporating the latest research advancements in antiviral therapy, comprehensive management, opportunistic infections, concurrent tumors, and the prevention and intervention of HIV infection. The new edition also introduces a new section on "Incomplete immune reconstitution", proposes the concept of "HIV vulnerable populations" for the first time with recommendations for their diagnosis and treatment. This edition of the Guidelines covers 14 sections: epidemiology, pathogenic characteristics, laboratory tests, pathogenesis, clinical presentation and staging, diagnostic criteria, common opportunistic infections, antiretroviral therapy, immune reconstitution inflammatory syndrome, incomplete immune reconstitution, AIDS-related neoplasms, prevention of mother-to-child transmission and conception in serodiscordant couples, pre- and post-exposure prophylaxis, and whole-course management of HIV infection. This edition of the Guidelines aims to assist clinical physicians in making informed decisions in the diagnosis, treatment, and management of HIV/AIDS and will be periodically revised and updated based on domestic and international research progress.

Keywords: Acquired immune deficiency syndrome; Diagnosis; Guideline; Human immunodeficiency virus; Treatment

Acquired immunodeficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV), is one of the major public health threats. The first edition of the *Chinese Guidelines for the Diagnosis and Treatment of HIV/AIDS* was formulated in 2005 by the Acquired Immunodeficiency Syndrome Professional Group of Society of Infectious Diseases of the Chinese Medical Association. The guidelines were updated in 2011, 2015, 2018, and 2021.[1] The 2024 edition of the Guidelines is revised on the basis of the 2021 edition and updated according to the national clinical practice and the latest research results. The Guidelines aim to assist clinical physicians in making informed decisions in the diagnosis, treatment, and management of HIV/AIDS. However, they are not mandatory standards and cannot cover all issues in HIV/AIDS diagnosis and treatment. The Acquired Immunodeficiency Syndrome Professional Group will periodically revise and update the Guidelines based on domestic and international research progress.

The recommendations in this edition of Guidelines are based on scientific research evidence and expert opinions. The capital letters (A, B, or C) and Arabic numerals (1 or 2) following each recommendation indicate the quality of evidence and the strength of the recommendation, respectively, as shown in Supplementary Table 1, http://links.lww.com/CM9/C219 (graded according to the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] system).

1. Epidemiology

1.1 Source of infection

People living with HIV/AIDS (PLWHA)

HIV predominantly presents in the body fluids of PLWHA, including blood, semen, vaginal secretions, pleural effusions, ascites, cerebrospinal fluid, amniotic fluid, breast milk, etc.

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1.2 Routes of HIV infection and transmission

HIV transmission occurs through sexual contact (including unprotected homosexual, heterosexual, and bisexual contact), blood or blood products (including intravenous drug use with needle sharing, unsafe and substandard invasive medical procedures, or tattoos), and mother-to-child transmission (including intrauterine transmission, intrapartum transmission, and transmission through breastfeeding).

Vulnerable populations: Men who have sex with men (MSM), people who inject drugs, sexual partners of PLWHAs, people with multiple sexual partners, and people with sexually transmitted infections (STIs) are at high risk of acquiring HIV.

1.3 Case reporting

HIV voluntary counseling and testing has been implemented. Newly diagnosed HIV/AIDS cases should be immediately reported to the local Center for Disease Control and Prevention, in accordance with the Law of the People's Republic of China on Prevention and Control of Infectious Diseases. Corresponding measures should be taken to manage the reported cases under the guidelines set for Class B infectious diseases.

1.4 Medical management

Follow the principle of confidentiality and implement full-course management measures, including the following: strengthening follow-up of PLWHA; providing timely, standardized, and comprehensive treatment, which includes antiretroviral therapy (ART) and symptomatic supportive care; and offering necessary medical and psychological counseling (including education and measures regarding the prevention of further HIV transmission).

1.5 Prevention

PLWHA should use condoms correctly and engage in safe sex; they should also refrain from drug use, needle and syringe sharing. Moreover, voluntary blood donation should be promoted, with mandatory HIV screening among blood donors. Hospital management should be reinforced to strictly follow disinfection procedures and control nosocomial infections. Infections via occupational exposure should be prevented. Efforts should be made to eliminate mother-to-child transmission. Provider-initiated HIV testing and counseling should be provided to spouses and sexual partners of PLWHA, children of PLWHA, intravenous drug users with whom PLWHA shared needles and syringes, and people who engaged in high-risk behaviors and/or clinical symptoms of HIV infection. People at high risk of HIV infection should receive antiviral drugs for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) after providing written informed consent and ensuring high adherence.

Recommendation 1: Healthcare personnel should proactively offer HIV-related testing and corresponding counseling services to spouses and sexual partners of PLWHA, intravenous drug users who share needles with PLWHA, children born to PLWHA, and clinical patients with high-risk behaviors for HIV infection and/or clinical symptoms (C1).

2. Pathogenic Features

HIV is a human lentivirus belonging to the lentivirus genus and the retroviridae family. The spherical virus measures between 100 nm and 120 nm in diameter. It comprises an interior viral core and outer viral envelope. The viral core is formed by the capsid protein (CA, p24) containing two identical single-stranded, positive-sense HIV RNA molecules, nucleocapsid protein, and enzymes necessary for viral replication, including reverse transcriptase (RT, p51/p66), integrase (IN, p32), and protease (PR, p10). The exterior coat of HIV is the viral envelope, with embedded envelope glycoprotein gp120, and transmembrane glycoprotein gp41. The viral matrix protein (MA, p17) underlies the enveloped virion, forming the inner shell of the virus.

HIV is classified into two types: HIV-1 and HIV-2. The HIV genome is approximately 9.7 kb in length. Long terminal repeats (LTRs) are situated at each end of the genome and are involved in the regulation of HIV gene integration and expression, as well as viral replication. The HIV genome contains three structural genes (*gag*, *pol*, and *env*), two regulatory genes (*tat* [transactivator of transcription] and *rev* [regulator of expression of virion proteins]), and four auxiliary genes (*nef* [negative regulatory factor], *vpr* [viral protein r], *vpu* [viral protein u], and *vif* [viral infectivity factor]). Among these, *vpu* is unique to HIV-1 and *vpx* is unique to HIV-2.

HIV is highly variable, with *env* ranking first among all mutable genes. The major contributors to this variability include: random mutations resulting from the lack of proofreading ability in RT, a high viral replication rate, host immune selection, gene recombination between viral DNA and host DNA, and drug selection. Non-standard ART and poor adherence to ART are the major contributing factors for drug resistance.

HIV-1 is the major epidemic strain in China. The HIV-2 subtype is mainly concentrated in West Africa and has not yet spread worldwide; however, several PLWHA with HIV-2 infection have been identified since 1999 in parts of China followed by reports of imported HIV-2 cases in multiple regions, which deserve closer attention.[2]

The main receptors involved in HIV-1 entry into host cells are CD4 molecules expressed on the surface of T lymphocytes, mononuclear macrophages, and dendritic cells. HIV enters cells via receptors on the surface of susceptible cells. The receptors include the primary receptor (CD4, major receptor) and co-receptors (such as CCR5 and CXCR4).

The process of HIV infection in human cells includes: (1) Adsorption, membrane fusion, and penetration: After HIV-1 infects the human body, it selectively attaches to the CD4 receptor of the target cell and enters the host cell with the assistance of auxiliary receptors. (2) Reverse

transcription, nuclear entry, and integration: In the cytoplasm, RT converts the viral RNA genome into complementary DNA (cDNA) molecules. These cDNA molecules are then synthesized into linear double-stranded DNA and subsequently enter the cell nucleus. Once inside the nucleus, this DNA is integrated into the chromosomal DNA of the host cell (a process mediated by integrase). The viral DNA integrated into the host DNA is referred to as a "provirus". (3) Transcription and translation: When the provirus is activated and begins transcription, the viral DNA is transcribed into RNA by cellular RNA polymerase. This RNA is then translated into viral structural proteins (Gag, Gag-Pol, and Env precursor proteins) and various non-structural proteins on the ribosomes in the cell nucleus. (4) Assembly, budding, and maturation: The process of virus assembly is complex and highly ordered. Gag and Gag-Pol precursor proteins and the virus's progeny RNA genomes are packaged on the inner surface of the cellular membrane. Meanwhile, gp120 and gp41 are transported to the surface of the cellular membrane bind to the Gag and matrix protein as they bud from the membrane. As a result, the virions acquire their envelopes from the cellular membrane during budding and become independent virus particles.

3. Laboratory Tests[3]

The primary laboratory tests for HIV/AIDS include HIV antibody tests, HIV antigen-antibody tests, HIV nucleic acid tests, CD4$^+$ T lymphocyte count, and HIV drug resistance tests. HIV antibody or antigen-antibody tests are usually used initially for screening. Confirmatory supplementary tests include HIV-1/2 antibody test and HIV nucleic acid testing (qualitative and quantitative). The HIV nucleic acid quantitation and CD4$^+$ T lymphocyte count are two important indicators of disease progression, clinical treatment, efficacy, and prognosis. Finally, HIV genotypic drug resistance testing can provide references for the selection and changes in ART regimens.

3.1 HIV antibody test or HIV antigen-antibody test

HIV antibody tests can simultaneously detect HIV-1/2 antibodies. HIV antigen-antibody tests can detect both HIV-1/2 antibodies and antigens. Common tests for antibodies or antigen-antibody combinations include enzyme-linked immunosorbent assay (ELISA), chemiluminescence assays, immunofluorescence assays, and rapid tests. Confirmatory antibody tests typically use immunoblot assays, strip/line immunoassays, and other methods that specifically detect HIV antibodies.

3.1.1 Screening test

If the screening test result is non-reactive, report "negative for HIV-1/2 antibody" or "negative for HIV antigen-antibody", indicating that the individual is not infected with HIV. However, during the window period, patients with HIV infection might also receive negative screening test results. If the screening test result is reactive, repeat the test using two samples (for rapid tests)/two spots of the original reagent (chemiluminescent assay or enzyme-linked immunoassay) or two different reagents. If both tests are non-reactive, report "negative for HIV-1/2 antibody" or "negative for HIV antigen-antibody"; if either or both of the tests are reactive, a confirmatory test should be performed.

3.1.2 Confirmatory test of antibodies

Antibody confirmatory tests without HIV-specific bands are reported as "negative for HIV-1/2 antibody". If HIV-specific bands appear but do not meet the diagnostic criteria, the results are reported as "HIV antibody inconclusive", followed by nucleic acid testing or follow-up visit in 2–4 weeks to determine the presence of HIV antibodies based on the results of nucleic acid or subsequent tests. Confirmatory tests of HIV antibodies with positive results are reported as "positive HIV-1/2 antibody confirmed".

3.2 CD4$^+$ T lymphocyte assays

CD4$^+$ T lymphocytes are the primary target cells of HIV infection. After HIV infection, a progressive loss of CD4$^+$ T lymphocytes occurs, resulting in an inverted ratio of CD4$^+$/CD8$^+$ T lymphocytes and impaired cellular immune function.

Flow cytometry is commonly used to assess CD4$^+$ T lymphocyte subgroups. The clinical significance of CD4$^+$ T lymphocyte count includes determining the immune status, monitoring disease progression, assisting with disease staging, assessing treatment efficacy, and predicting the occurrence of clinical complications.

The intervals at which CD4$^+$ T lymphocyte counts are assessed should be decided by clinicians based on the specific conditions of patients. CD4$^+$ T lymphocyte counts should be performed once before treatment, once 3 months after ART initiation, and every 3–6 months within the first 2 years of treatment. For patients with baseline CD4$^+$ T lymphocyte counts <200–350/μL, it is recommended to be tested once every 3 months. For those with counts >350/μL at baseline, testing should be conducted once every 6 months. After 2 years of treatment, patients with CD4$^+$ T lymphocyte count between 350/μL and 500/μL whose HIV infection is fully suppressed by ART are recommended to undergo testing once every 12 months. Patients with CD4$^+$ counts >500/μL can undergo testing by discretion. In cases of delayed ART initiation, changes in drug regimen due to ART failure, and viral loads >200 copies/mL in repeated tests in the treatment process, patients are recommended to be tested once every 3–6 months. Testing should be performed at regular intervals for patients experiencing virological breakthrough, AIDS-related clinical symptoms, or receiving therapies that may reduce CD4$^+$ T lymphocyte counts, based on the patient's clinical condition.

The inverted CD4$^+$/CD8$^+$ T lymphocyte ratio can be improved to varying degrees with the prolonged use of ART. The inversion is closely associated with the timing of treatment initiation and baseline CD4$^+$ T lymphocyte counts, suggesting the treatment efficacy and patient's immune-inflammatory status.[4]

3.3 HIV nucleic acid testing

Common methods for HIV nucleic acid testing include real-time polymerase chain reaction and transcription-mediated amplification (TMA). Currently, HIV nucleic acid testing in China targets only HIV-1 and cannot detect HIV-2.

3.3.1 Nucleic acid supplementary test

Both qualitative and quantitative HIV-1 nucleic acid tests can be used as supplementary tests. It is recommended to use qualitative tests as the first choice for supplementary testing. HIV-1 qualitative nucleic acid testing includes the detection of RNA or DNA. If the result is reactive, it is reported as "HIV-1 nucleic acid positive"; if the result is non-reactive, it is reported as "HIV-1 nucleic acid negative". For quantitative HIV-1 nucleic acid testing, if the result is below the detection limit, it is reported as below the detection limit; if it is >1000 copies/mL, the detected value is reported. For results above the detection limit but ≤1000 copies/mL, re-sampling and testing are recommended. Clinicians can combine epidemiological history, clinical manifestations, $CD4^+$ and $CD8^+$ T lymphocyte counts, or HIV antibody supplementary test follow-up results to confirm or exclude diagnosis. HIV nucleic acid testing is particularly valuable for diagnosing patients in the acute phase/window period and late stage.

3.3.2 Monitoring the effectiveness of ART[5]

Quantitative HIV-1 nucleic acid testing of the viral load in the peripheral blood can be used to evaluate the effectiveness of ART and guide adjustments in ART regimens. One test should be performed before initiating ART, and if ART is not initiated promptly, regular testing is recommended. After treatment initiation, the first test should be conducted approximately 4–8 weeks after starting treatment, followed by testing every 8–12 weeks until the viral load is below the detection limit. If the virus is stably suppressed, testing is recommended every 3–4 months within the first 2 years of treatment; after 2 years of treatment, testing is recommended every 6 months. If the ART regimen is adjusted due to treatment failure, the first viral load test should be conducted 4–8 weeks after the adjustment, followed by testing every 8–12 weeks until the viral load is below the detection limit. If the ART regimen is changed due to drug toxicity or simplification of the regimen for individuals with viral suppression, viral load testing should be conducted 4–8 weeks after the adjustment to confirm viral load suppression. If the viral load is >200 copies/mL during treatment, testing is recommended every 3 months. Patients with emerging AIDS-related clinical symptoms or those undergoing glucocorticoid or cancer chemotherapy should have viral load tested every 3 months.

3.4 HIV genotypic resistance testing

The results of HIV drug resistance testing can provide a reference for ART regimen initiation and adjustment. Drug resistance testing includes genotypic and phenotypic assays. Globally, the most predominantly used methods are genotypic assays. HIV genotypic resistance testing is performed before initiating ART and when the treatment regimen needs to be altered due to an unsatisfactory reduction in viral load or virological failure post-treatment. For patients experiencing ART failure, drug-resistance testing should be performed while they are still receiving antiretrovirals; if antiretrovirals have been discontinued, the test should be performed within 4 weeks after discontinuation.

For treatment-naive patients, genotypic resistance testing before initiating ART should be based on the local prevalence of transmitted drug resistance. Standard baseline genotypic resistance testing should primarily focus on detecting gene mutations in RT and protease. For newly diagnosed people or those who test HIV-positive following receipt of long-acting injectable cabotegravir (CAB-LA) as PrEP, if there is concern about resistance to integrase strand transfer inhibitor (INSTIs), genotypic mutation testing of the integrase gene should be conducted.[5,6]

Recommendation 2: For individuals with a positive HIV screening test, further confirmation of HIV infection should be conducted through supplementary tests, including antibody supplementary tests (HIV-1/2 antibody confirmatory test) and nucleic acid supplementary tests (HIV-1 qualitative and quantitative nucleic acid tests) (A1).

Recommendation 3: For treatment-naive patients, genotypic resistance testing should be performed before initiating ART. For newly diagnosed individuals or those who become HIV-positive after using long-acting injectable cabotegravir (CAB-LA) as PrEP, if there is a concern about resistance to INSTIs, genotypic mutation testing of the integrase gene should be conducted (C1).

4. Pathogenesis

HIV attacks the human immune system, particularly $CD4^+$ T lymphocytes, mononuclear macrophages, and dendritic cells, leading to a decline in $CD4^+$ T cell counts. This results in weakened cellular immunity, increasing vulnerability to opportunistic infections and cancers. Additionally, HIV raises the risk of conditions such as cardiovascular diseases (CVDs), bone disorders, kidney issues, and liver problems.

Once inside the body, HIV reaches regional lymph nodes within 1–2 days and is detectable in the blood within about 5–10 days. It then causes viremia, marked by a quick decrease in $CD4^+$ T cell counts. Without treatment, these cell counts often return to normal or near-normal levels. However, because the body cannot fully eliminate HIV due to viral reservoirs, chronic infection ensues, which may be symptomatic or asymptomatic. HIV reduces $CD4^+$ T cell counts through direct destruction during replication, cell death mechanisms like apoptosis and pyroptosis, atrophy of thymic tissue and death of thymic cells, and indirectly via inflammation or immune system destruction. HIV also causes dysfunction and abnormal immune activation of $CD4^+$ T lymphocytes, B

lymphocytes, mononuclear macrophages, natural killer (NK) cells, and dendritic cells.

Clinical HIV progression can be typical, rapid, or slow. Factors affecting progression include viral characteristics, the host's immune state, and genetic makeup.

For most people with HIV/AIDS treated with ART, their immune systems can largely recover, restoring $CD4^+$ T cell counts and immune functions. Yet, between 10% and 40% of these individuals do not fully regain their immune health, despite effective viral suppression. These individuals, known as immunological non-responders, face higher risks of both AIDS-related and non-AIDS-related illnesses and mortality.[7]

5. Clinical Presentation and Staging

HIV disease progression is a long, complex process from initial infection to end-stage disease. The different stages of disease progression are characterized by varying clinical presentations related to HIV. HIV disease progression can be categorized into three stages: acute infection, asymptomatic infection, and AIDS, based on the clinical manifestations observed post-infection.

5.1 Acute infection

Acute infection usually occurs within 6 months after HIV infection. Some people with HIV infection show clinical symptoms caused by viremia and acute immune system injury during the acute phase. Fever is the most common clinical presentation. Sore throat, night sweats, nausea, vomiting, diarrhea, rash, arthralgia, lymphadenopathy, and neurological symptoms may also present. The clinical symptoms are usually mild and improved after 1–3 weeks for most patients.

During this period, HIV RNA and p24 antigen can be detected in the blood. HIV antibodies seroconversion can be observed within 2–3 weeks, accompanied by a transient drop in $CD4^+$ T lymphocyte count, an inverted $CD4^+/CD8^+$ T lymphocyte ratio, and abnormal T cell immune activation. Some patients may experience mild leukopenia, thrombocytopenia, or liver function abnormalities.

5.2 Asymptomatic infection

Following the symptomatic or asymptomatic acute infection, patients enter the asymptomatic infection stage. This stage generally lasts from 4 years to 8 years, with variations based on the viral load, viral strain, routes of infection, individual differences in immunological status, nutritional conditions, lifestyle, and other factors. During this stage, persistent HIV replication compromises the immune system, leading to the gradual decline of $CD4^+$ T lymphocyte count and an inverted $CD4^+/CD8^+$ T lymphocyte ratio. Symptoms or signs, such as lymphadenopathy, can also appear. Clinically, it is necessary to consider the epidemiological history to achieve early detection and timely diagnosis.

5.3 AIDS

AIDS is the final stage of HIV infection. The $CD4^+$ T lymphocyte count falls below 200/μL in most patients with AIDS. The major clinical presentations during this stage include HIV-related symptoms and signs, and various opportunistic infections and tumors.

6. Diagnostic Criteria[8]

6.1 Diagnostic principles

The diagnosis of HIV/AIDS should be based on a comprehensive and careful analysis of patient epidemiological history (including unsafe sex practice, intravenous drug use, transfusion of unscreened blood or blood products, being a child born to an HIV-positive mother, or occupational exposure to HIV), clinical presentation, and laboratory findings. HIV antibody tests and pathogenic assays assist in confirming the diagnosis of HIV infection. Epidemiological history is an important reference for diagnosing acute HIV infection or HIV infection in infants. $CD4^+$ T lymphocyte count and clinical presentation are the major criteria for staging HIV infection. AIDS-defining illnesses serve as critical indicators for the diagnosis of AIDS. Individuals diagnosed with HIV infection but who have not progressed to AIDS are referred to as people living with HIV, whereas "AIDS patients" specifically denotes those whose HIV infection has advanced to AIDS.

HIV infection in adults, adolescents, and children aged >18 months can be diagnosed if one of the following criteria is met: (1) A positive HIV antibody screening test and positive a HIV confirmatory test (a positive confirmatory antibody test, a positive qualitative nucleic acid test, or a quantitative nucleic acid testing >1000 copies/mL); (2) Recent epidemiological history or AIDS-related clinical presentations and two positive HIV nucleic acid tests; and (3) HIV seropositivity.

For children aged <18 months, HIV infection can be diagnosed if one of the following criteria is met: (1) Children born to HIV-positive women and two positive HIV nucleic acid tests (the second sampling and test need to be performed 4 weeks after birth); (2) A history of iatrogenic exposure, HIV seropositivity, or two positive HIV nucleic acid tests; and (3) Children born to HIV-positive mothers and HIV seropositivity.

6.2 Diagnostic criteria for early stage (phase I) HIV infection

Phase I HIV infection in adults and adolescents aged ≥15 years can be diagnosed if any of the following criteria are met: (1) An epidemiological history within the past 3–6 months, symptoms of acute HIV infection syndrome, and/or persistent generalized lymphadenopathy (PGL); (2) Negative antibody screening results and a positive reaction to two nucleic acid tests; and (3) Evidence of HIV seroconversion within 1 year. The diagnosis of phase I HIV infection for HIV-positive children aged <15 years should be based on $CD4^+$ T lymphocyte counts and associated clinical presentations.[8]

6.3 Diagnostic criteria for mid-stage (phase II) HIV infection

Phase II HIV infection in HIV-positive adults and adolescents aged ≥15 years can be diagnosed if one of the following criteria is met: (1) A $CD4^+$ T lymphocyte count between 200/μL and 500/μL; (2) Absence of symptoms or presentation of clinical symptoms associated with the asymptomatic infection stage. The diagnosis of phase II HIV infection for HIV-positive children aged <15 years should be based on $CD4^+$ T lymphocyte counts and associated clinical presentations.[8]

6.4 Diagnostic criteria for AIDS (phase III)

HIV-positive adults and adolescents aged ≥15 years can be diagnosed with AIDS if one of the following criteria is met: (1) Persistent irregular fever (>38°C) of unknown origin for >1 month; (2) Diarrhea (>3 times/day) for >1 month; (3) Unexplained weight loss >10% of body weight within 6 months; (4) Recurrent oral fungal infections; (5) Recurrent herpes simplex virus or zoster virus infections; (6) Pneumocystis pneumonia (PCP); (7) Recurrent bacterial pneumonias; (8) Active tuberculosis or non-tuberculosis mycobacteria (NTM) infections; (9) Deep fungal infections; (10) Space-occupying lesions in the central nervous system; (11) Dementia in young and middle-aged adults; (12) Active Cytomegalovirus (CMV) infection; (13) Cerebral toxoplasmosis; (14) *Talaromyces marneffei* infection; (15) Recurrent septicemia; and (16) Kaposi's sarcoma, lymphoma. These individuals can also be diagnosed with AIDS if HIV infection is confirmed and the $CD4^+$ T lymphocyte count is <200/μL.

Children aged <15 years can be diagnosed with AIDS if one of the following criteria is met: HIV infection and $CD4^+$ T lymphocyte percentage <25% (aged <12 months), <20% (aged 12–36 months), or <15% (aged 37–60 months), or a $CD4^+$ T lymphocyte count <200/μL (5–l4 years of age); or HIV infection accompanied by at least one AIDS-defining illness in children.

Recommendation 4: The entire course of HIV infection can be divided into three stages: the acute infection phase, the asymptomatic infection phase, and the AIDS phase. The diagnosis of HIV/AIDS requires a comprehensive analysis that combines epidemiological history, clinical manifestations, and laboratory test results. Diagnoses should be made cautiously, and clinical staging should be performed (A1).

7. Common Opportunistic Infections[9]

7.1 PCP

7.1.1 Diagnosis

(1) Subacute onset, presenting as progressive fever, dry cough, and shortness of breath after exertion, and respiratory distress may occur in severe cases. (2) Lung examinations may reveal positive signs, such as sporadic rhonchi or rales. These signs are usually disproportionate to the symptom severity. (3) Chest radiographs show diffuse reticular nodule-like interstitial infiltration in both lungs starting from the hilus. Lung computed tomography (CT) shows ground-glass change in bilateral lungs. Patients with a prolonged clinical course may exhibit varying degrees of interstitial lung fibrosis. The imaging findings of PCP often lag behind the clinical deterioration or improvement of symptoms.[10] Concurrent bacterial or mycobacterial infections are present in 13–18% of patients and can manifest with corresponding pulmonary imaging findings. (4) Arterial blood-gas analysis shows hypoxemia and significantly decreased arterial partial pressure of oxygen (PaO_2) in severe cases, often <60 mmHg (1 mmHg = 0.133 kPa). (5) Blood lactate dehydrogenase levels usually >350 U/L and can reflect the dynamic changes in the disease.[11,12] Plasma (1, 3)-β-d-glucan (BDG) levels notably higher than normal,[13] and the trend of these changes can be used as a predictor of the effectiveness of PCP treatment.[14] (6) Confirmed diagnosis depends on the identification of the pathogen in sputum or bronchovesicular lavage/lung biopsy specimens, in which pneumocystis cysts or trophozoites may be found. PCR is also an alternative diagnostic method.[15]

7.1.2 Treatment

(1) Symptomatic treatment: bed rest, supplemental oxygen, and balanced intake of water and electrolytes. (2) Pathogen treatment: The first-line regimen is oral sulfamethoxazole-trimethoprim (SMZ-TMP, SMZ 400 mg and TMP 80 mg/tablet). For mild-moderate cases, TMP 15–20 $mg \cdot kg^{-1} \cdot day^{-1}$, SMZ 75–100 $mg \cdot kg^{-1} \cdot day^{-1}$. (3) Divided into 3–4 doses daily for 21 days is recommended and can be prolonged when necessary.[16] For severe cases, the same dosage is recommended to be given intravenously, and can be prolonged when necessary. For patients with SMZ-TMP allergy, desensitization therapy can be attempted. Alternative treatments include: (1) Clindamycin (600–900 mg, IV, every 8 h, or 450 mg, PO, every 6 h), in combination with primaquine (15–30 mg, PO, q.d. for 21 days); (2) Oral dapsone (100 mg, q.d.) combined with oral TMP (15–20 $mg \cdot kg^{-1} \cdot day^{-1}$, divided into 3–4 doses daily) for 21 days; and (3) Pentamidine (3–4 $mg \cdot kg^{-1} \cdot day^{-1}$, q.d., slow IV drip [longer than 60 min]) for 21 days. (4) Glucocorticoid therapy: For patients with moderate to severe PCP (PaO2 <70 mmHg or alveolar-arterial PO_2 difference >35 mmHg), glucocorticoid therapy can be initiated in the early stage (within 72 h). The recommended dosage for oral prednisone is 40 mg b.i.d. for 5 days, followed by 20 mg b.i.d. for another 5 days, and then 20 mg q.d. for 11 days, making a total treatment duration of 21 days. If intravenous methylprednisolone is used, the dose should be 75% of the equivalent prednisone dose. (5) Assisted ventilation: Assisted ventilation can be administered in patients with progressive dyspnea. (6) ART: ART should be initiated as soon as possible, usually within 2 weeks after initiation of anti-PCP treatment.

7.1.3 Prophylaxis

(1) Prophylaxis indications: $CD4^+$ T lymphocyte count <200/μL (adults, adolescents, pregnant women, and patients on ART). (2) Medications: The first-line regimen

choice is SMZ-TMP (1 and 2 tablets/day for primary and secondary prophylaxis, respectively). In patients who cannot tolerate or have an allergy to the medication, the alternative is dapsone. Patients with PCP receiving ART treatment can discontinue medications for PCP prophylaxis when their CD4$^+$ T lymphocyte count is >200/μL for ≥3–6 months. If CD4$^+$ T lymphocyte counts drop again to <200/μL, prophylaxis should be reinitiated. Patients with PCP receiving ART treatment can also consider discontinuing the medications for PCP prophylaxis when their CD4$^+$ T lymphocyte count is 100–200/μL with an undetectable viral load for 3–6 months.

Recommendation 5: For the treatment of PCP, the first choice remains SMZ-TMP. The recommended dosage is TMP 15–20 mg·kg^{-1}·day^{-1} and SMZ 75–100 mg·kg^{-1}·day^{-1}, divided into 3–4 doses/day for a treatment duration of 21 days. For severe patients (PaO_2 <70 mmHg or alveolar-arterial oxygen gradient >35 mmHg), early glucocorticoid therapy (within 72 h) with prednisone or intravenous methylprednisolone can be administered, with a total glucocorticoid treatment duration of 21 days (A1).

Recommendation 6: HIV/AIDS patients with a CD4$^+$ T lymphocyte count <200/μL should use SMZ-TMP for PCP prophylaxis. Primary prophylaxis is 1 tablet/day, and secondary prophylaxis is 2 tablets/day. Prophylaxis can be discontinued after ART if the CD4$^+$ T lymphocyte count rises to >200/μL and remains at that level for ≥3–6 months (A1).

7.2 Tuberculosis

7.2.1 Diagnosis[17]

Tuberculosis can occur in patients with HIV/AIDS at any level of CD4$^+$ T lymphocyte counts.The diagnosis of HIV/AIDS and tuberculosis co-infection should be based on a comprehensive analysis of clinical presentations and the results of auxiliary, pathological, microbiological and imaging examinations. Patients with higher CD4$^+$ T lymphocyte counts present clinical manifestations similar to those of ordinary tuberculosis patients, while those with lower CD4$^+$ T lymphocyte counts often present with extrapulmonary tuberculosis or disseminated tuberculosis. In terms of tuberculosis diagnosis, the World Health Organization (WHO) guidelines[18]recommend the use of rapid molecular assays, including Xpert MTB/RIF and Xpert MTB/RIF Ultra, as the initial test for tuberculosis diagnosis. Acid-fast staining, culture, rapid molecular assays such as Xpert MTB/RIF, and histopathologic examinations are the main methods for confirming tuberculosis.

7.2.2 Treatment

Patients with HIV/AIDS and tuberculosis should receive routine treatment regimens for tuberculosis; however, drug interactions and incompatibility between antituberculosis and antiretroviral medications should be considered.

The anti-tuberculosis medications mainly include isoniazid, rifampicin, rifabutin, ethambutol, and pyrazinamide. If the *Mycobacterium tuberculosis* infection is susceptible to first-line anti-tuberculous agents, then isoniazid + rifampicin (or rifabutin), ethambutol, and pyrazinamide should be used for 2 months for intensive therapy, followed by the use of isoniazid + rifampicin (or rifabutin) for 4 months for consolidation.

Studies have shown that a 4-month short-course regimen containing rifapentine and moxifloxacin (rifapentine + moxifloxacin + isoniazid + pyrazinamide for the first 2 months, followed by rifapentine + moxifloxacin + isoniazid for the subsequent 2 months) is not inferior in efficacy to the traditional 6-month regimen for treating drug-sensitive pulmonary tuberculosis.[19,20] The World Health Organization (WHO) guidelines have recommended the 4-month short-course regimen for the treatment of pulmonary tuberculosis.[21,22] For patients with a delayed response to anti-tuberculosis treatment (i.e., those who still have tuberculosis-related clinical manifestations or positive *Mycobacterium tuberculosis* cultures after 2 months of treatment) and for those with bone and joint tuberculosis, the duration of anti-tuberculosis treatment should be extended to 9 months. For patients with central nervous system tuberculosis, the treatment duration should be extended to 9–12 months.

All patients with HIV/AIDS and tuberculosis should receive ART regardless of CD4$^+$ T lymphocyte counts. As immune reconstitution inflammatory syndrome (IRIS) rarely leads to death, current recommendations indicate that patients with HIV co-infection with tuberculosis should start ART as early as possible (ART initiation within 2 weeks after anti-tuberculosis treatment initiation is recommended).[5,9,21,23] If the patient has drug-resistant tuberculosis (including multidrug resistant tuberculosis [MDR-TB] and extensive drug resistant tuberculosis [XDR-TB]), ART should be started within 8 weeks after beginning second-line anti-tuberculosis medications. For patients with central nervous system tuberculosis, it is generally recommended to initiate ART 4–8 weeks after starting anti-tuberculosis treatment. For patients with tuberculous meningitis, glucocorticoids are usually recommended. In patients with AIDS and tuberculous meningitis who are using glucocorticoids, it is recommended to start ART within 2 weeks after initiating anti-tuberculosis treatment.[6]

Patients co-infected with HIV and tuberculosis need to be closely monitored for adverse drug reactions and drug–drug interactions. If necessary, the dose of antiviral or anti-tuberculosis agents should be adjusted or therapeutic drug monitoring (TDM) performed to guide treatment interventions.

Recommendation 7: HIV/AIDS patients should undergo systematic tuberculosis screening at each visit. Clinicians should consider the patient's history, typical symptoms and signs of tuberculosis, as well as imaging and laboratory tests, to systematically screen for tuberculosis (B1).

Recommendation 8: The principles of tuberculosis treatment in HIV/AIDS patients are the same as for general tuberculosis patients. However, attention should be paid to drug interactions and contraindications between anti-tuberculosis drugs and antiretroviral drugs (A1).

Recommendation 9: All HIV/AIDS patients with coexisting tuberculosis, regardless of their CD4$^+$ T lymphocyte count, should start ART as early as possible, preferably within 2 weeks of beginning anti-tuberculosis treatment. For patients with drug-resistant tuberculosis, ART should be initiated within 8 weeks after starting second-line anti-tuberculosis medications. For patients with central nervous system tuberculosis, ART is generally recommended to be initiated 4–8 weeks after starting anti-tuberculosis treatment (C1). For AIDS patients with tuberculous meningitis who are on glucocorticoids, it is recommended to start ART within 2 weeks of beginning anti-tuberculosis treatment.

7.3 NTM infection

HIV/AIDS can be complicated by NTM infection, with *Mycobacterium avium complex* (MAC) infection being the most common one.

7.3.1 Diagnosis

MAC infection has similar clinical symptoms as active tuberculosis except for a high frequency of systemic dissemination that involves multiple organs, with presentations of fever, anemia, hepatosplenomegaly, and generalized lymphadenopathy. Confirmed diagnosis depends on the detection of NTM in blood culture, lymph node culture, bone marrow culture, or culture of other sterile tissues or body fluid.

7.3.2 Treatment

The first-line treatment regimen for MAC infection is: clarithromycin (500 mg b.i.d [or azithromycin 500 mg/day] + ethambutol [15 mg·kg^{-1}·day^{-1}] combined with rifabutin [300–600 mg/day]).[9,24] For patients with severe infection and severe immunosuppression (CD4$^+$ T lymphocyte count <50/μL), amikacin (10 mg·kg^{-1}·day^{-1}, IM, q.d,) or fluoroquinolone antibiotics, such as levofloxacin or moxifloxacin, may be administered together. The treatment usually lasts for at least 12 months. Treatment of other NTM infections should be adapted based on the identification of bacterial strains and the results of drug susceptibility.[23] ART should be started as soon as possible, usually 2 weeks after the initiation of anti-MAC therapy.

Recommendation 10: HIV/AIDS patients with co-infections of NTM are primarily infected with MAC. The diagnosis of MAC infection relies on culturing MAC from the patient's blood, lymph nodes, bone marrow, or other sterile tissues or body fluids (A1).

Recommendation 11: The preferred treatment regimen for MAC disease includes clarithromycin 500 mg b.i.d. (or azithromycin 500 mg q.d.) combined with ethambutol 15 mg·kg^{-1}·day^{-1} and rifabutin (300–600 mg q.d.). For patients with severe infection and significant immunosuppression (CD4$^+$ T lymphocyte count <50/μL), additional medications such as amikacin (10 mg·kg^{-1}·day^{-1}, IM, q.d.) or fluoroquinolone antibiotics like levofloxacin or moxifloxacin can be added (B1). The treatment duration is typically at least 12 months. ART should be initiated as soon as possible, preferably within 2 weeks after starting anti-MAC treatment (B1).

7.4 CMV infection

As the most common herpes virus infection in patients with HIV/AIDS, CMV infection can be categorized as CMV viremia or CMV infection with organ involvement. CMV infection can involve multiple organ systems, including the eyes, lungs, digestive system, central nervous system, among which CMV retinochoroiditis is the most common manifestation in patients with HIV/AIDS.

7.4.1 Diagnosis and treatment of CMV retinitis

Diagnosis

The typical symptoms include muscae volitantes, floating objects in vision, blind spots, and peripheral vision impairment. Patients with CMV retinitis usually present with rapid vision deterioration, "scrambled eggs and ketchup" appearance lesion in fundus examinations, and dense and yellowish-white retinal lesions along the blood vessels with or without intraretinal hemorrhage. The confirmed diagnosis depends on the fundoscopic exam.

Treatment

Recommended systemic therapy regimen: (1) Ganciclovir (5 mg/kg, IV drip, q12h for 14–21 days), then 5 mg/kg IV drip, q.d.; (2) Ganciclovir (5 mg/kg, IV drip, q12h for 14–21 days), then oral valganciclovir (900 mg, q.d.) or ganciclovir 1.0 g, t.i.d.; and (3) Oral valganciclovir (900 mg, q12h for 14–21 days), then 900 mg, q.d. or oral ganciclovir 1.0 g, t.i.d. Alternative treatment regimen: foscarnet sodium (60 mg/kg, IV drip, q8h or 90 mg/kg, IV drip, q12h, 14–21 days), then 90 mg/kg IV drip, q.d., or oral ganciclovir (1.0 g, t.i.d.). Topical treatment: Topical treatment requires the involvement of ophthalmologists for the administration of intravitreal injection of ganciclovir (2 mg per injection) or foscarnet (2.4 mg per injection) once weekly until the retinal lesions are controlled or inactive.

7.4.2 Diagnosis and treatment of CMV infections in other sites

The clinical presentations of CMV pneumonia include fever, cough, dyspnea, and interstitial changes on chest radiographs. The diagnosis of CMV pneumonia is challenging and mainly depends on clinical symptoms, radiographic changes, and pathologic findings (CMV inclusion bodies observed in pulmonary tissues or cells). Meanwhile, other

common pathogens associated with pneumonia must be excluded. Intravenous infusions of ganciclovir, foscarnet sodium, or ganciclovir combined with foscarnet sodium are recommended as treatment regimens; however, the therapy course is yet to be confirmed. CMV esophagitis or enteritis: presents as fever, dysphagia or odynophagia, diarrhea, watery stools, or watery stools mixed with blood, accompanied by abdominal pain. Ulceration of the mucous membrane can be observed on gastroscopy or enteroscopy, and CMV inclusion bodies can be observed in histopathological examinations. Treatment: medications as above. The therapy course lasts for 3–4 weeks or until relief of symptoms and signs. CMV encephalitis presents as neuropsychiatric alterations, lethargy, insanity, confusion, dullness, aphasia, visual impairment, inertia, epileptic seizure, facial paralysis, and others. The diagnosis of CMV encephalitis depends on the detection of CMV DNA in the cerebrospinal fluid or brain tissue by polymerase chain reaction (PCR), with a sensitivity of 80% and a specificity of 90%. Treatment regimen: Ganciclovir is used in combination with foscarnet sodium for 3–6 weeks (dosage same as above), followed by maintenance therapy until the results of quantitative CMV assay of cerebrospinal fluid are negative. Therapy regimens should be personalized based on specific conditions.

7.4.3 ART

ART should be started as early as possible (within 2 weeks after initiation of anti-CMV treatment).

7.4.4 Prophylaxis

Primary prophylaxis is not recommended for CMV infection. Fundoscopic examinations should be regularly performed for patients with $CD4^+$ T lymphocyte counts <200/μL. Once CMV infection occurs, it should be actively treated. The prophylaxis regimen should be continued even after CMV retinitis lesions become inactive. Ganciclovir (1.0 g, PO, t.i.d.,) is usually used to prevent the reactivation of the CMV infection. Discontinuation of prophylaxis can be considered if $CD4^+$ T lymphocyte count is >100/μL for >3 to 6 months in response to ART. Secondary prophylaxis is not recommended for CMV enteritis, CMV pneumonia, and CMV neuropathy.

Recommendation 12: The diagnosis of CMV retinitis relies on ophthalmoscopic examination. Treatment options include ganciclovir, valganciclovir, and foscarnet, with a course of 2–3 weeks. For local treatment, intravitreal injections of ganciclovir or foscarnet can be administered once a week until the retinal lesions are controlled and inactive (A1).

Recommendation 13: Primary prophylaxis for CMV infection is not recommended for HIV/AIDS patients. The preferred secondary prophylaxis regimen is oral ganciclovir (1.0 g, three times daily). Secondary prophylaxis can be considered for discontinuation when the $CD4^+$ T lymphocyte count exceeds 100/μL and remains stable for more than 3–6 months (B1).

7.5 Herpes simplex virus or varicella zoster virus infections[2,5]

7.5.1 Diagnosis

Herpes simplex and varicella zoster virus infections can usually be diagnosed based on their typical clinical presentations. Diagnosis can also be confirmed by PCR and viral culture of the collected blister fluids.

7.5.2 Treatment

The main medications are acyclovir, famciclovir, valaciclovir, and foscarnet sodium. Acyclovir or foscarnet sodium are recommended for the treatment of HIV infection complicated by varicella zoster virus infection. (1) The treatment courses for oral herpes simplex and genital herpes simplex last for 5–10 days and 5–14 days, respectively. The treatment regimen is oral acyclovir (400 mg, t.i.d.). (2) Severe mucosal herpes simplex: acyclovir (5 mg/kg, IV drip, q8h), then oral acyclovir (400 mg, t.i.d.) once the damaged mucosa begins to heal. The medications should be discontinued after the lesion completely heals. (3) For patients with herpes simplex resistant to acyclovir, foscarnet sodium (40 mg/kg, IV drip, q8h or q12h) is recommended until the disease is cured. (4) Localized herpes zoster: acyclovir (5–10 mg/kg, IV drip, q8h for 7 days). (5) Severe mucocutaneous herpes zoster: foscarnet sodium (40 mg/kg, IV drip, q8h or q12h) or acyclovir (10 mg/kg, IV drip, q8h), then oral valaciclovir (1.0 g, t.i.d.) after the patient is medically stable and until the lesions disappear. (6) Acute retinal necrosis: acyclovir (10 mg/kg, IV drip, q8h), then oral valaciclovir (1.0 g, t.i.d.) after the patient is medically stable. (7) ART: initiate ART as soon as possible after anti-herpes treatment.

7.6 Cerebral toxoplasmosis

7.6.1 Diagnosis

The clinical presentations of cerebral toxoplasmosis include fever and localized or diffuse damage to the central nervous system. Cranial CT scans show one or more low-density sites appearing as rings or nodules in contrast enhancement, frequently surrounded by edema. Cranial magnetic resonance imaging shows multiple long T1 and long T2 signals. Positron emission tomography (PET) is helpful for clinical diagnosis. Immunological-based techniques adopted to detect toxoplasma antibodies in serum or interstitial fluid specimens are auxiliary methods of diagnosing toxoplasmosis. Diagnosis may be confirmed by brain biopsy.

7.6.2 Treatment

Pathogen treatment: (1) The first-line regimen of choice is pyrimethamine (loading dose 100 mg, PO, b.i.d., and 50–75 mg/day for subsequent maintenance) + sulfadiazine (1–1.5 g, PO, 4 times/day). (2) Alternative treatment: SMZ-TMP (3 tablets, PO, t.i.d.) combined with clindamycin (600 mg, IV, q6h) or azithromycin (0.5 g, q.d.). The therapy course lasts for at least 6 weeks. (3) Symptomatic

treatment: Reduction of intracranial pressure, anticonvulsant therapy, antiepileptic therapy, etc. (4) ART: initiate ART as soon as possible within 2 weeks after anti-toxoplasmosis treatment.

7.6.3 Prophylaxis

For HIV-positive patients without a history of cerebral toxoplasmosis but with CD4+ T lymphocyte counts <200/μL and positive toxoplasma IgG results, a prescription of SMZ-TMP (2 tablets, q.d.) for prophylaxis purposes is generally indicated. After ART initiation, prophylaxis can be stopped when the CD4+ T lymphocyte count increases to >200/μL and remains so for more than 3 months. Alternatively, if the CD4+ T lymphocyte count is between 100/μL and 200/μL and the viral load remains persistently below the detection limit for 3–6 months, prophylaxis can also be considered for discontinuation. For patients who have had cerebral toxoplasmosis, the long-term use of pyrimethamine (25–50 mg/day) + sulfadiazine (2–4 g/day) for prophylaxis is needed until the CD4+ T lymphocyte count increases to >200/μL for ≥6 months. Prophylaxis should be restarted if the CD4+ T lymphocyte count drops to <200/μL.

Recommendation 14: The first-choice treatment for toxoplasmic encephalitis is pyrimethamine (loading dose of 100 mg, PO, b.i.d., followed by 50–75 mg q.d. for maintenance) in combination with sulfadiazine (1–1.5 g, PO, four times a day). Alternative treatment includes SMZ-TMP (3 tablets, PO, t.i.d.) with either clindamycin (600 mg, IV, every 6 h) or azithromycin (0.5 g/day). The treatment course should be at least 6 weeks (A1).

Recommendation 15: HIV/AIDS patients without a history of toxoplasmic encephalitis but with a CD4+ T lymphocyte count <200/μL and positive toxoplasma IgG antibodies should use SMZ-TMP (2 tablets q.d.) to prevent toxoplasmic encephalitis (B1). After ART initiation, prophylaxis can be stopped when the CD4+ T lymphocyte count increases to >200/μL and remains so for more than 3 months (A1). Alternatively, if the CD4+ T lymphocyte count is between 100/μL and 200/μL and the viral load remains persistently below the detection limit for 3–6 months, prophylaxis can also be considered for discontinuation (B1).

Recommendation 16: For patients with a history of toxoplasmic encephalitis, long-term prophylaxis with pyrimethamine (25–50 mg/day) combined with sulfadiazine (2–4 g/day) should be used until the CD4+ T lymphocyte count increases to >200/μL and remains so for ≥6 months (A1). If the CD4+ T lymphocyte count drops below 200/μL, prophylactic treatment should be restarted (C1).

7.7 Fungal infection

7.7.1 Diagnosis

Candida and *Cryptococcus neoformans* infections are the more common fungal infections occurring in clinical practice. *T. marneffei* infection is also common in Southern China or humid and rainy regions. The diagnosis of fungal infection depends on the clinical presentation, pathogens found in cultures of infected site biopsy specimens, or the results of pathological examinations. *C. neoformans* infection predominantly occurs in patients with CD4+ T lymphocyte counts <100/μL. Cryptococcus antigen latex agglutination tests of blood or cerebrospinal fluid specimens can assist with the diagnosis of *C. neoformans* infection. Meningitis or meningoencephalitis due to Cryptococcus mainly manifests in clinical practice as fever, progressive headache, psychiatric and neurological symptoms. Increased intracranial pressure (ICP) with severe headache, nausea, and vomiting is also common clinical presentations. Staining of cerebrospinal fluid smears reveals cryptococci under the light microscope. *T. marneffei* infection predominantly occurs in patients with CD4+ T lymphocyte counts <50/μL, presenting as fever, anemia, cough, rash, generalized lymphadenopathy, hepatosplenomegaly and centrally pitting rash. A confirmed diagnosis depends on the detection of *T. marneffei* in blood culture, bone marrow culture, and culture of other sterile body fluids. Tests for *T. marneffei*-specific mannoprotein (Mp1p) and galactomannan (GM) can assist with rapid diagnosis.[26]

7.7.2 Treatment

(1) *Candida* infection

Oral *Candida* infections.[27] The first-line regimen is oral fluconazole (100–200 mg/day for 7–14 days). Alternative treatment regimen: oral itraconazole solution (200 mg, q.d., for 7–14 days) or topical nystatin and mouthwash containing sodium bicarbonate. For esophageal *Candida* infection, we recommend oral or intravenous fluconazole (100–400 mg/day) or oral voriconazole (200 mg, b.i.d.) for 14–21 days. For patients with oropharyngeal or esophageal fungal infections, ART should be initiated as soon as possible and antifungal therapy can be concomitantly administered with ART.

(2) *C. neoformans* infection

Meningitis or meningoencephalitis due to cryptococcus.[9,28,29] Principles of pathogen treatment: The treatment regimen is divided into the induction, consolidation, and maintenance phases (reference: *Expert Consensus on the Diagnosis and Treatment of Cryptococcal Meningitis*[28] and *International Guideline on the Clinical Diagnosis and Treatment for Cryptococcosis*[29]) [Table 1]. The classical regimen for the induction therapy is amphotericin B + 5-flucytosine. Start amphotericin B at 0.02–0.1 $mg \cdot kg^{-1} \cdot day^{-1}$ and gradually raise to 0.5–0.7 $mg \cdot kg^{-1} \cdot day^{-1}$. Amphotericin B frequently leads to adverse reactions; therefore, close monitoring is necessary. The induction phase lasts for at least 4 weeks, followed by consolidation with fluconazole (600–800 mg/day) for at least 6 weeks after improvement of clinical symptoms and conversion of cerebrospinal fluid culture from positive to negative. Subsequently, patients are switched to maintenance with fluconazole (200 mg/day) for at least 1 year, until those on ART

Table 1: Antifungal regimens for cryptococcal meningitis or meningoencephalitis.

Treatment phase	Antifungal medications		Course of treatment
	First-line	Second-line	
Induction	Amphotericin B (0.5–0.7 mg·kg^{-1}·day^{-1}) + flucytosine (100 mg·kg^{-1}·day^{-1})	Amphotericin B (0.5–0.7 mg·kg^{-1}·day^{-1}) + fluconazole (600–800 mg/day)	≥4 weeks
	Liposomal amphotericin B (3–4 mg·kg^{-1}·day^{-1}) + flucytosine (100 mg·kg^{-1}·day^{-1})	Amphotericin B (0.5–0.7 mg·kg^{-1}·day^{-1})	
		Fluconazole (600–800 mg/day) ± Flucytosine (100 mg·kg^{-1}·day^{-1})	
		Itraconazole injection (days 1–2, loading dose 200 mg, q12h; starting from day 3, 200 mg, q.d.) ± flucytosine (100 mg·kg^{-1}·day^{-1})	
		Voriconazole (day 1 loading dose 6 mg/kg, q12h; starting from day 2 mg/kg, 4 mg/kg, q12h) ± flucytosine (100 mg·kg^{-1}·day^{-1})	
		Amphotericin B cholesterol sulfate complex (3–4 mg·kg^{-1}·day^{-1}) + flucytosine (100 mg·kg^{-1}·day^{-1})	
	A single dose of liposomal amphotericin B (10 mg/kg) combined with 2 weeks of flucytosine (100 mg·kg^{-1}·day^{-1}) and fluconazole (1200 mg/day for adults; 12 mg·kg^{-1}·day^{-1} for children and adolescents, with a maximum dose of 800 mg/day).		2 weeks
Consolidation	Fluconazole (600–800 mg/day) ± flucytosine (100 mg·kg^{-1}·day^{-1})	Itraconazole oral solution (200 mg, q12h) ± flucytosine (100 mg·kg^{-1}·day^{-1})	≥6 weeks
	Amphotericin B (0.5–0.7 mg·kg^{-1}·day^{-1}) ± flucytosine (100 mg·kg^{-1}·day^{-1})	Voriconazole tablets (200 mg, q12h) ± flucytosine (100 mg·kg^{-1}·day^{-1})	
	Liposomal amphotericin B (3–4 mg·kg^{-1}·day^{-1}) ± flucytosine (100 mg·kg^{-1}·day^{-1})		
		Amphotericin B cholesterol sulfate complex (3–4 mg·kg^{-1}·day^{-1}) ± flucytosine (100 mg·kg^{-1}·day^{-1})	
Maintenance	Fluconazole 200 mg/day	Itraconazole 400 mg/day	≥1 year

show CD4$^+$ T lymphocyte counts of >100/μL for at least 6 months. ICP lowering treatment: Patients with elevated ICP must receive active ICP lowering treatment. The commonly used methods for ICP-lowering include medication, lumbar puncture drainage, lumbar cistern drainage, external drainage of lateral ventricle, ventriculoperitoneal shunt, placement of an Ommaya reservoir, etc. When using glucocorticoids to reduce ICP, be aware of the risk of CMV infection.[30] Aseptic techniques should be strictly applied during continuous external drainage for ICP reduction. Close monitoring and care are required to prevent secondary infections.

Pulmonary cryptococcosis. The recommended treatment regimen for diffuse pulmonary cryptococcal infection is the same as for central nervous system infections. For localized pulmonary cryptococcal infection: oral fluconazole (400–800 mg/day for 10 weeks), followed by maintenance with oral fluconazole (200 mg/day). The antifungal therapy course lasts for 6 months in total.

Cryptococcal antigenemia.[9,21] For patients positive for qualitative serum cryptococcal antigen, oral fluconazole (400–800 mg/day for 10 weeks) is recommended, followed by maintenance oral fluconazole (200 mg/day). The therapy course lasts for 6–12 months in total.

ART: HIV-positive patients with cryptococcal pneumonia should receive ART after 2 weeks of anti-cryptococcal therapy. For HIV-positive patients with cryptococcal meningitis, premature ART might be associated with a higher mortality rate; thus, properly deferred ART can be considered (ART is generally initiated after 4–6 weeks of standard anti-cryptococcal therapy).[21,31] For some individuals, ART needs to be started in advance, although it is best to ensure that ART is initiated after negative cerebrospinal fluid culture tests are obtained.[29,32]

(3) *T. marneffei* infection

Antifungal therapy induction phase: Regardless of disease severity, the first-line regimen is amphotericin B (0.5–0.7 mg·kg^{-1}·day^{-1}) or liposomal amphotericin B (3–5 mg·kg^{-1}·day^{-1}, IV drip) or amphotericin B cholesterol sulfate complex 3–4 mg·kg^{-1}·day^{-1} for 2 weeks.[33–35] Patients who cannot tolerate amphotericin B can receive an alternative regimen comprising voriconazole IV drip or oral voriconazole as follows: 6 mg/kg (loading dose) q12h on day 1, then 4 mg/kg, q12h for >2 weeks.[33] Consolidation phase: oral itraconazole or voriconazole 200 mg, q12h for 10 weeks in total. Subsequently, secondary prophylaxis is conducted: oral itraconazole (200 mg, q.d.). The discontinuation of prophylaxis can be considered for patients on

ART treatment with CD4+ T lymphocyte counts >100/μL for at least 6 consecutive months.[36] Once the CD4+ T lymphocyte count is <100/μL, prophylaxis therapy must be restarted.[34] ART can be started within 1–2 weeks after the initiation of effective antifungal therapy.

Recommendation 17: For the treatment of cryptococcal meningitis in HIV/AIDS patients, the therapy is divided into three phases: induction, consolidation, and maintenance. The preferred regimen for the induction phase is amphotericin B (0.5–0.7 $mg \cdot kg^{-1} \cdot day^{-1}$) or liposomal amphotericin B (3–4 $mg \cdot kg^{-1} \cdot day^{-1}$) combined with flucytosine (100 $mg \cdot kg^{-1} \cdot day^{-1}$) for at least 4 weeks. During the consolidation phase, fluconazole is used (600–800 mg/day) for at least 6 weeks. The maintenance phase involves fluconazole (200 mg/day) for at least 1 year, continuing until the patient's CD4+ T lymphocyte count exceeds 100/μL and remains so for at least 6 months after ART (A1).

Recommendation 18: For the induction treatment of cryptococcal meningitis in HIV/AIDS patients, a single dose of liposomal amphotericin B 10 mg/kg combined with 2 weeks of flucytosine (100 $mg \cdot kg^{-1} \cdot day^{-1}$) and fluconazole (600–800 mg/day) is recommended (A1).

Recommendation 19: For HIV/AIDS patients with cryptococcal meningitis, ART should be initiated 4–6 weeks after the start of appropriate antifungal therapy (A1).

Recommendation 20: For HIV/AIDS patients with cryptococcal antigenemia, it is recommended to administer fluconazole 400–800 mg/day PO for 10 weeks, followed by 200 mg/day PO as preventive treatment. The total duration of therapy should be 6–12 months (C1).

Recommendation 21: For the treatment of talaromycosis in HIV/AIDS patients, the preferred induction phase antifungal regimen is amphotericin B (0.5–0.7 $mg \cdot kg^{-1} \cdot day^{-1}$), liposomal amphotericin B (3–5 $mg \cdot kg^{-1} \cdot day^{-1}$), or amphotericin B cholesterol sulfate complex (3–4 $mg \cdot kg^{-1} \cdot day^{-1}$), administered intravenously for 2 weeks (A1). The consolidation phase involves oral itraconazole or voriconazole 200 mg every 12 h for 10 weeks. This is followed by secondary prophylaxis with oral itraconazole 200 mg once daily (B1) until the patient's CD4+ T lymphocyte count exceeds 100/μL and remains so for at least 6 months after ART (B1). If the CD4+ T lymphocyte count falls below 100/μL, prophylactic treatment should be restarted (C1).

8. ART

8.1. Treatment objectives

To minimize HIV replication, decrease the viral load to the lower limit of detection, reduce virus mutation, restore immune function, reduce abnormal immune activation, contain transmission, and prevent mother-to-child transmission, and reduce the incidence and mortality of HIV infection and non-AIDS-related illnesses, so that PLWHA can achieve normal life expectancy with improved quality of life.

8.2. Antiretrovirals currently available in China

Globally, over 40 antiretroviral drugs (ARVs) in seven classes are currently available: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTIs), fusion inhibitors (FIs), CCR5 inhibitors, and capsid inhibitors. The ARVs available in China belongs to five classes: NRTIs, NNRTIs, PIs, INSTIs, and FIs (including single-tablet regimens [STRs]).

8.3. Timing and first-line regimens for ART in adults and adolescents[5,21,23,37]

8.3.1 Timing for ART initiation in adults and adolescents

Once the diagnosis of HIV infection is confirmed, immediate ART initiation is recommended regardless of CD4+ T lymphocyte counts. Before ART initiation, patient adherence and consent must be obtained and the patient must be well-educated on medication compliance. For eligible patients, rapid ART initiation (within 7 days of diagnosis) or ART initiation on the same day as diagnosis can be considered.

Recommendation 22: All HIV-positive individuals, regardless of their CD4+ T lymphocyte counts, should start ART as early as possible to reduce morbidity and mortality and to prevent HIV transmission (B1). For patients with the necessary conditions, it is recommended to initiate ART rapidly (within 7 days of diagnosis) or on the same day as diagnosis (A1).

8.3.2 First-line ART regimens for adults and adolescents

The recommended first-line regimens comprise two NRTIs (backbone medications) combined with a third class of drugs. The third class of drugs includes INSTIs, NNRTIs, or boosted PIs (containing ritonavir or cobicistat). A STR can also be adopted. Table 2 lists the recommended first-line ART regimens and alternative regimens for adults and adolescents based on antiretroviral medications available in China.

Recommendation 23: For treatment-naive adult patients, the recommended ART regimen typically consists of two NRTI backbone drugs combined with a third drug, which can be an INSTI, a NNRTI, or a boosted PI (containing ritonavir or cobicistat). An STR can also be selected (A1). For treatment-naive patients who are hepatitis B surface antigen (HBsAg) negative and have a viral load of $<5 \times 10^5$ copies/mL, the ART regimen of dolutegravir/lamivudine can be the first choice (A1).

8.4. ART for special populations

8.4.1 Children[21,38]

ART should be initiated as soon as possible in HIV-positive children. Without timely ART initiation, AIDS-related

Table 2: Recommended first-line ART regimens for adults and adolescents.

Regimens	Details	
Recommended Regimens	2 NRTIs	Third class of drugs
	TDF + 3TC (FTC) FTC/TAF	+NNRTIs: EFV[†], RPV[‡]
		Or + PIs: DRV/c, LPV/r
		Or + INSTIs: DTG, RAL
	STR	
	BIC/FTC/TAF[*]	
	EVG/c/FTC/TAF[*]	
	DTG/ABC[§]/3TC[*]	
	DOR/3TC/TDF[*]	
	ANV/3TC/TDF[*]	
	1 NRTI + 1 INSTIs	
	DTG/3TC[‖] or DTG + 3TC[‖]	
Alternative		
	AZT(ABC) + 3TC	+NNRTIs: EFV or RPV or DOR or ANV or NVP[¶]
		Or + PIs: LPV/r, DRV/c
		Or + INSTIs: DTG, RAL
	TDF + 3TC (FTC)FTC/TAF	+NNRTIs: NVP[¶]
	TDF + Azvudine[**]	+NNRTIs: EFV

[*]STR. [†]EFV not recommended for patients with viral loads >5 × 10^5 copies/mL. [‡]RPV only used in patients with viral load <10^5 copies/mL and CD4+ T lymphocyte count >200/μL. [§]Used in patients negative for HLA-B5701. [‖]DTG + 3TC and DTG/3TC are used in patients tested negative for HBsAg with viral load <5 × 10^5 copies/mL. [¶]For patients with baseline CD4+ T lymphocyte counts >250/μL, regimens containing NVP should be avoided where possible; for patients co-infected with HCV, regimens containing NVP should be avoided. [**]Conditionally approved Chinese generic drugs used in combination with NRTIs and NNRTIs for adult patients with high viral load (≥10^5 copies/mL). 3TC: Lamivudine; ABC: Abacavir; ANV: Ainuovirine; ART: Antiretroviral therapy; AZT: Zidovudine; BIC: Bictegravir; DOR: Doravirine; DRV/c: Darunavir/cobicistat; DTG: Dolutegravir; EFV: Efavirenz; EVG/c: Elvitegravir/cobicistat; FTC: Emtricitabine; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B irus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HLA: Human leukocyte antigen; INSTIs: Integrase strand transfer inhibitors; LPV/r: Lopinavir/ritonavir; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NRTIs: Nucleoside reverse transcriptase inhibitors; NVP: Nevirapine; PIs: Protease inhibitors; RAL: Raltegravir; RPV: Rilpivirine; STR: Single-tablet regimen; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.

mortality rates can reach 20–30% in the first year after birth and over 50% in the second year.

Timing of ART initiation and regimens for HIV-positive children: Once HIV diagnosis is confirmed for children, immediate ART initiation is recommended regardless of CD4+ T lymphocyte counts. If ART cannot be initiated, children's immunologic, virologic, and clinical status must be closely monitored at a recommended frequency of once every 3–4 months.

The recommended first-line ART regimens for children is two NRTIs (backbone medications) combined with a third class of drugs, which can be INSTIs or NNRTIs or boosted PIs (containing ritonavir or cobicistat). Table 3 lists the recommended regimens in detail based on China's current clinical practices.

Monitoring of ART efficacy in children infected with HIV: (1) Viral load is the primary measure of ART efficacy. After 6 months of ART, viral load testing should be performed once annually or when ART failure is suspected. (2) CD4+ T lymphocyte count is another useful indicator of ART efficacy. CD4+ T lymphocyte counts should be performed once every 3–6 months; however, these results by itself cannot be used to determine ART success or failure. (3) Clinical monitoring is an essential component of monitoring in HIV-positive children. Height, weight, growth markers, and adherence must be monitored during each follow-up visit.

Management of first-line ART failure in children: After first-line ART failure, the regimen should be adjusted based on the results of drug resistance testing. (1) For children experiencing failure of first-line NNRTIs-based regimens, the treatment should be switched to dolutegravir (DTG) or bictegravir (BIC), or boosted PIs + 2 NRTIs (preferred PIs: Lopinavir/ritonavir [LPV/r]). (2) Failure on a first-line LPV/r-based regimen does not generally occur due to the resistance to LPV/r. Drug adherence should be improved instead, and the viral load can be tested after 3 months. If the viral load is still not suppressed, the treatment should be switched to DTG (or BIC) + 2 NRTIs. If DTG is unavailable, raltegravir (RAL) + 2 NRTIs should be used. If both DTG and RAL are unavailable, children aged <3 years can be maintained on their initial treatment regimen and educated on drug adherence, while children aged ≥3 years can be switched to NNRTIs + 2 NRTIs (preferred NNRTI: efavirenz (EFV)). (3) Substitution of NRTIs in case of treatment failure: ABC or tenofovir disoproxil fumarate (TDF) can be substituted with zidovudine (AZT), while AZT can be substituted with TDF or abacavir (ABC).

Recommendation 24: Once children are diagnosed with HIV infection, it is recommended to initiate ART immediately, regardless of CD4+ T lymphocyte counts (B1).

Recommendation 25: For treatment-naive children, the recommended ART regimen consists of two NRTI backbone drugs combined with a third drug, which can be an INSTI, a NNRTI, or a boosted PI (containing ritonavir or cobicistat) (B1).

8.4.2 Pregnant women

Please refer to Section 12 on "Prevention of mother-to-child (or vertical) HIV Transmission and Reproductive Options for HIV-serodiscordant Couples".

8.4.3 Lactating women

Breastfeeding involves the risk of HIV transmission; thus, HIV-positive women should avoid breastfeeding where

Table 3: ART regimens for children.

Age	Recommended regimen	Alternative regimen	Descriptions
0–4 weeks after birth	ABC (or AZT) + 3TC + RAL	ABC (or AZT) + 3TC + NVP (or LPV/r)	1. Due to rapid drug metabolism in very young infants and their high viral load correlated with the immaturity of their immune system, highly potent regimens are required for ART in infants; 2. RAL can be used for infants with a body weight of ≥2 kg. 3. For infants with previous exposure to NNRTIs, LPV/r should be used.
Children aged 4 weeks to 3 years	ABC + 3TC + DTG; BIC/FTC/TAF	ABC (or AZT) + 3TC + NVP (or RAL or LPV/r)	1. DTG can be used for infants over 4 weeks with a body weight of ≥3 kg. The recommended dosage for dispersible tablets (5 mg/tablet) are as follows: 3–6 kg: 5 mg, 6–10 kg: 15 mg, 10–14 kg: 20 mg, 14–20 kg: 25 mg, ≥20 kg: 30 mg. All doses are administered once daily. 2. For children aged ≥2 years and with a body weight of ≥14 kg, BIC/FTC/TAF can be chosen. When using an ART regimen containing NNRTI or INSTI, the two NRTI backbone drugs can be FTC/TAF. 3. For children with a body weight of ≥35 kg using an ART regimen containing PI/r, the two NRTI backbone drugs can be FTC/TAF. 4. TDF cannot be used for children aged <2 years
Children aged ≥3 years and adolescents	ABC + 3TC + DTG (or EFV), or BIC/FTC/TAF	TDF (or AZT) + 3TC + NVP (or LPV/r、or RAL), or EVG/c/FTC/TAF	1. DTG film-coated tablets can be used for children with a body weight of ≥14 kg. The recommended doses are as follows: for body weight ≥14 kg and less than 20 kg: 40 mg once daily; for body weight ≥20 kg: 50 mg once daily. Note that film-coated tablets and dispersible tablets are not interchangeable at equal doses. 2. For children with a body weight of ≥25 kg, EVG/c/FTC/TAF can be an alternative. 3. For children with a body weight of ≥35 kg, DOR can be an alternative.

3TC: Lamivudine; ABC: Abacavir; ART: Antiretroviral therapy; AZT: Zidovudine; BIC/FTC/TAF: Bictegravir/emtricitabine/tenofovir alafenamide; BIC: Bictegravir; DOR: Doravirine; DTG: Dolutegravir; EFV: Efavirenz; EVG/c/FTC/TAF: Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FTC/TAF: Emtricitabine/Tenofovir alafenamide; INSTI: Integrase strand transfer inhibitor; LPV/r: Lopinavir/ritonavir; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside reverse transcriptase inhibitor; NVP: Nevirapine; PI/r: Boosted protease inhibitor; RAL: Raltegravir; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.

possible. In particular, breastfeeding is not recommended for women whose viral load remains detectable. If the mother insists on breastfeeding, the ART regimen must be maintained during the entire lactation period (consistent with the ART regimen used during pregnancy) and breastfeeding should not be continued beyond 6 months.

8.4.4 PLWHA co-infected with *Mycobacterium tuberculosis*

For details on the timing of ART initiation, please refer to "7.2 *tuberculosis*", "Diagnosis and prophylaxis of common opportunistic infections". The recommended first-line ART regimens for HIV/AIDS patients co-infected with tuberculosis are TDF (AZT) + lamivudine (3TC) (or emtricitabine [FTC]) + EFV, or regimens including INSTIs.[5,21,23] Previous studies[39] showed that while DTG-based ART regimens can be used in patients with HIV co-infected with tuberculosis, the dose of DTG needed to be increased (50 mg, b.i.d.) when co-administered with rifampicin. Since clinical studies on patients with HIV co-infected with tuberculosis did not indicate the non-inferiority of RAL-containing ART regimens to EFV-containing regimens in terms of antiviral efficacy, RAL is usually only used for AIDS patients co-infected with tuberculosis who cannot tolerate other ART regimens.[40,41] An increase in the dose of RAL (800 mg, b.i.d.) is recommended when co-administered with rifampicin. Since rifabutin is a weaker inducer of liver enzymes, substitution of rifampicin with rifabutin can be considered in patients with HIV on DTG or RAL who are co-infected with tuberculosis, with no need for dose adjustment. If the above-mentioned ART regimens are not available, FIs-containing ART regimens can be used. Co-administration of INSTIs (BIC or elvitegravir [EVG/c]) with rifamycins is not recommended. If rifabutin is used for antituberculosis treatment, PIs-based ART regimens can also be used.

Recommendation 26: For HIV/AIDS patients co-infected with tuberculosis, the recommended first-line ART regimen is TDF (or AZT) + 3TC (or FTC) + EFV, or DTG (A1). When co-administered with rifampicin, the dose of DTG should be doubled (50 mg, b.i.d.) (A1).

8.4.5 Intravenous drug users on methadone maintenance therapy

The timing of ART initiation for intravenous drug-using patients is the same as that for other patients; however, substance abuse may affect patients' adherence to medications. Thus, before initiating ART, patients must be adequately informed that medication adherence is a primary determinant of treatment success. STRs or fixed-dose combination regimens should be used where possible and preference of INSTIs or FIs-containing ART regimens can be considered for eligible patients. Medication adherence can be effectively improved by continuous monitoring of drug distributions. Moreover, drug interactions between antiretroviral medications and methadone should be considered.

8.4.6 PLWHA co-infected with hepatitis B virus (HBV)

In individuals with no indication for the deferred initiation of ART, ART should be started as soon as possible regardless of $CD4^+$ T lymphocyte counts. (1) HIV-positive patients co-infected with HBV require the administration of HIV/HBV co-treatment that includes 2 anti-HBV medications. The recommended NRTI backbones are TDF (or tenofovir alafenamide [TAF]) + 3TC (or FTC). However, TAF is associated with a lower incidence of renal toxicity and osteoporosis compared to TDF.[42] (2) Regimens containing only one NRTI with anti-HBV activity (TDF, 3TC, entecavir, telbivudine, and adefovir) are not recommended for HIV-positive patients co-infected with HBV, due to the risk of inducing HIV resistance to NRTIs. (3) Studies have shown that in HIV/HBV co-infected patients, BIC/FTC/TAF is not inferior in terms of viral suppression compared to FTC/TDF + DTG. Additionally, the BIC/FTC/TAF treatment group had higher rates of hepatitis B e antigen (HBeAg) seroconversion, HBeAg seroclearance, and HBsAg seroclearance.[43] (4) HBV-associated indicators should be monitored during treatment, including HBV DNA, hepatic biochemical biomarkers, hepatic imaging, and HBV drug-resistance. Clinicians should be aware of the occurrence of hepatic cirrhosis and hepatocelullar carcinoma.

The following should be noted for patients with renal insufficiency[44]: (1) If the estimated glomerular filtration rate (eGFR) is <60 $mL \cdot min^{-1} \cdot 1.73\ m^2$, TDF should not be selected or the dose of TDF needs to be adjusted. (2) If the eGFR is <60 $mL \cdot min^{-1} \cdot 1.73\ m^2$ and >30 $mL \cdot min^{-1} \cdot 1.73\ m^2$, regimens containing TAF can be considered. The use of TAF in patients with eGFR <30 $mL \cdot min^{-1} \cdot 1.73\ m^2$ has yet to be approved. (3) When TDF/TAF is not accessible, entecavir should be added to the ART regimen.

Recommendation 27: For HIV/HBV co-infected patients, regardless of $CD4^+$ T lymphocyte counts, it is recommended to initiate ART as early as possible. The ART regimen should include two antiviral drugs with activity against HBV. The recommended nucleoside backbone drugs in the ART regimen are TDF (or TAF) + 3TC (or FTC) (B1).

8.4.7 PLWHA co-infected with hepatitis C virus (HCV)

ART regimens for patients infected with HIV alone can serve as a reference for ART regimens in patients with HIV/HCV co-infections. However, the following points should be considered: (1) ARVs with less hepatic toxicity are recommended. The preference of INSTIs- or FIs-based ART regimens can be considered for eligible patients. (2) Anti-HCV therapies are recommended for HIV patients co-infected with HCV. The guidelines on HCV treatment can be used as a reference for regimens against HIV/HCV co-infection. The accumulation of drug toxicities and metabolism-based drug–drug interactions must be considered in the choice of medications, including switching to ART regimens with no interactions with anti-HCV drugs, as well as the consideration of short-term substitution with INSTIs or FIs. To avoid interactions between drugs with long half-lives, delaying anti-HCV treatment initiation for 2 weeks is recommended after changes in ART regimen. (3) ART initiation before anti-HCV treatment is recommended for patients with $CD4^+$ T lymphocyte counts $<200/\mu L$. Anti-HCV treatment can be started when the immune function has been restored to a certain level. Regardless of $CD4^+$ T lymphocyte counts, HIV/HCV co-infected patients can undergo anti-HCV treatment.[45]

Some studies have reported HBV reactivation induced by direct-acting antiviral agents (DAAs) administration and resulting in hepatic failure in patients infected with HIV/HBV/HCV. Hence, for patients with HIV/HBV/HCV infection, anti-HCV regimens with DAAs must be initiated after the patient is medically stable on an ART regimen containing medicines with anti-HBV activity. HIV patients co-infected with HCV need to be routinely screened for HBV markers before using DAAs.[46]

Recommendation 28: HIV/HCV co-infected patients should initiate ART as early as possible and actively undergo anti-HCV treatment. The regimen and duration of anti-HCV treatment should be the same as those for patients with HCV infection alone, with careful attention to potential drug interactions with ARVs (A1).

8.5 Monitoring of ART

Clinical assessments and laboratory tests need to be regularly performed during ART to evaluate its efficacy and to promptly identify the adverse effects of antiviral medications, as well as drug resistance. Medications should be promptly substituted based on these results to ensure ART success.

8.5.1 Evaluation of treatment efficacy

The effectiveness of ART can be evaluated according to virologic indicators, immunologic indicators, and clinical symptoms. Virologic changes are the most important indicators.

Virologic indicators: HIV plasma viral load should decrease by more than 1 log in most patients within 4 weeks after ART initiation and become undetectable after 3–6 months.

Immunologic indicators: Within 1 year after ART initiation, the CD4+ T lymphocyte count should increase by 30% or 100/μL compared with the baseline count, suggesting treatment effectiveness.

Clinical symptoms: After ART initiation, the incidence of opportunistic infections and the mortality rate due to HIV/AIDS are reduced significantly. Children show improvements in height, nutritional conditions, and physical development.

8.5.2 ARV

ARV resistance is one of the major causes of ART failure. Genotypic drug resistance testing can be performed in patients experiencing poor efficacy of ART or ART failure.

8.5.3 Monitoring of adverse drug effects

The adverse effects of ARVs comprise short-term and long-term adverse effects. In particular, adverse effects caused by the administration of some antiviral medications, including metabolic disorders, weight gain, osteoporosis, and hepatic/renal injury, need to be closely monitored, promptly identified, and properly managed. When necessary, ART regimens must be changed. The adverse effects of ARVs and their tolerability can affect medication adherence and, thus, ART efficacy; therefore, close monitoring and timely management of adverse effects are vital for improving treatment efficacy.

8.5.4 TDM

TDM can be used for special populations (such as children, pregnant women, and patients with renal insufficiency) when conditions allow.

Recommendation 29: After initiating ART, it is recommended to conduct virological, immunological, and clinical follow-ups every 3–6 months to evaluate the effectiveness of ART, promptly detect adverse effects of ARVs, and identify any emergence of viral resistance. This allows for timely medication adjustments to ensure the success of ART (C1).

8.6 Principles of drug substitution and ART for patients experiencing treatment failure[5,21,23,37]

8.6.1 ART for virologically-suppressed patients

Definition of virological suppression: HIV viral load below the lower limit of detection (<20 copies/mL or 50 copies/mL) after over 24 weeks of regular ART. In patients experiencing persistent virological suppression, ART regimens can be adjusted or optimized to specific needs. For more details, please refer to Section 14 on "Whole-course management of HIV infection."

8.6.2 ART for patients experiencing treatment failure

Definition of virological failure: For patients receiving continuous ART, virological failure is defined as plasma viral loads persistently >200 copies/mL 24 weeks after treatment initiation (initiation or adjustment) or virological rebound, which is defined as the recurrence of viral load >200 copies/mL after full virological suppression has been achieved.

When virological failure occurs, the patient's adherence to treatment, drug–drug interactions, and drug–food interactions should be evaluated first, especially medication adherence, which is the determinant of treatment success. ART regimens must be adjusted for patients experiencing ART failure based on the results of HIV drug resistance testing. The principles of regimen substitution include the substitution of at least two ART medications, and it is best to choose three drugs with antiviral activity (medications with antiviral activity can be selected from among previously used drugs, e.g., 3TC). The new ART regimens usually include a drug with full antiviral activity (boosted PIs or INSTIs) or a drug that has never been used with new mechanisms of action (e.g., capsid inhibitors, or FIs) or a combination of the above-mentioned medications.

8.6.3 Transient viral blips and low-level viremia (LLV)

After achieving virological suppression, a single detectable HIV RNA measurement followed by a return to virological suppression is termed a transient viral blip. It is generally considered that a single transient viral blip is not associated with subsequent virological failure. Transient viral blips are mostly not due to poor adherence but rather normal biological fluctuations or laboratory "artifacts".[47]

If two consecutive HIV RNA measurements are detectable between 50 copies/mL and 200 copies/mL, it is termed LLV. LLV requires an assessment of the patient's adherence, tolerability, drug adverse effects, and drug interactions. LLV usually does not require a change in the treatment regimen, but HIV RNA should be monitored every 3 months to evaluate whether an adjustment to the ART regimen is necessary.

8.7 Drug–drug interactions

Common ART medications interact with many other classes of drugs due to their metabolic pathways and toxicity. Concomitant medication use must be closely monitored in clinical practice and the medication regimen or dosage promptly adjusted based on relevant guidelines or medicine instructions.

Recommendation 30: It is recommended to use viral load testing as the primary method for detecting and confirming antiretroviral treatment failure (C1). Once antiretroviral treatment failure is confirmed, HIV resistance testing should be conducted as soon as possible (C1).

Recommendation 31: When virological failure occurs, the patient's treatment adherence, drug–drug, or drug–food interactions should be evaluated first, as adherence is a critical determinant of treatment success. For patients experiencing ART failure, the ART regimen should be adjusted based on the results of HIV resistance testing.

The principle for regimen selection is to replace at least two ART drugs, preferably three with antiviral activity. The new ART regimen should typically include one fully active boosted PI or INSTI, or a new drug with a novel mechanism of action, such as a capsid inhibitors or FI, or a combination of these drugs (A1).

Recommendation 32: LLV requires an assessment of the patient's adherence, tolerability, drug adverse effects, and drug interactions (A1). LLV usually does not necessitate a change in the treatment regimen (B1), but HIV RNA should be monitored every 3 months to evaluate whether an adjustment to the ART regimen is necessary (C1).

9. Immune Reconstitution Inflammatory Syndrome (IRIS)

9.1 Diagnosis

IRIS refers to a group of clinical syndromes that occur during the immune reconstitution following ART initiation in HIV-positive patients. This condition predominantly presents as fever, activation of latent infection, and aggravation or exacerbation of existing infection. IRIS is associated with a variety of latent or active opportunistic infections, such as tuberculosis and NTM infection, PCP or CMV infection, varicella zoster virus infection, toxoplasmosis, and cryptococcal infection, which can occur after ART initiation. In patients infected with HIV/HBV (or HCV), IRIS can manifest as viral hepatitis activation or exacerbation. IRIS generally occurs within 3 months after ART initiation and must be differentiated from HIV disease progression, primary or new opportunistic infections, and drug reactions. Apart from opportunistic infections, IRIS can also manifest as other diseases, such as sarcoidosis or Kaposi's sarcoma. In patients with advanced HIV infection co-infected with Mpox, worsening of the condition or death after ART initiation may also be related to IRIS.[48]The diagnostic criteria for IRIS[9,17] are as follows: (1) The clinical symptoms of opportunistic infections, including tuberculosis or cryptococcal meningitis, are exacerbated after the administration of ART. As the patient responds to ART, an exaggerated inflammatory response (usually detected through physical examination, imaging, or tissue biopsy) is observed, accompanied by an exacerbation of tuberculosis and enlargement of pre-existing lesions or the appearance of new lesions. Symptoms such as aggravated headache and increased ICP can manifest in patients with cryptococcal meningitis. (2) Exacerbation of clinical symptoms not associated with new opportunistic infections, HIV-associated cancers, adverse drug reactions, drug resistance, or treatment failure. (3) The viral load decreases and/or the $CD4^+$ T lymphocyte count increases after ART initiation.

9.2 Treatment[9,23]

Patients who develop IRIS should continue ART, except in severe, life-threatening cases of IRIS. IRIS manifesting as worsening of pre-existing infections is usually self-limiting and resolves spontaneously and, thus, does not require special treatment. IRIS manifesting as the reactivation of latent infections requires targeted anti-pathogenic treatment. In this context, corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) can be used for the short-term treatment of IRIS in severe cases. For patients with severe tuberculosis-related IRIS and severe IRIS associated with central nervous system diseases (such as tuberculous meningitis and progressive multifocal leukoencephalopathy), glucocorticoid therapy is recommended. Corticosteroids should be used with caution in patients with CMV infection and short-course oral corticosteroid therapy is recommended if needed. Patients receiving glucocorticoid therapy should be closely monitored for the occurrence of opportunistic infections, including CMV retinitis and tuberculosis.

9.3 Risk factors associated with IRIS

The risk factors associated with the appearance of IRIS include:[9] ART-naive patients, high baseline viral load, and low baseline $CD4^+$ T lymphocyte count. The incidence of IRIS can be lowered by effectively controlling acute opportunistic infections before ART initiation or by actively identifying and treating latent opportunistic infections before ART initiation.

Recommendation 33: When HIV-positive patients experience inflammatory-related presentations such as fever, activation of latent infections, or worsening of pre-existing infections after initiating ART, the diagnosis of IRIS should be considered. However, it is essential to rule out HIV disease progression, new infections, HIV-related tumors, drug adverse effects, and treatment failure. Clinically, based on the severity of IRIS, treatment for the related opportunistic infections should be initiated or continued. In severe cases, short-term use of glucocorticoids or NSAIDs may be considered (C1).

10. Incomplete Immune Reconstitution[49]

10.1 Diagnosis

After receiving effective ART, some AIDS patients with good viral control still fail to achieve normal $CD4^+$ T lymphocyte count.These patients are referred to as immunological non-responders (INR). According to this Guideline, the diagnostic criteria for INR are as follows: after more than 4 years of ART, with peripheral blood viral load below the detection limit (<50 copies/mL) for over 3 years, the $CD4^+$ T lymphocyte count remains below 350/μL. Additionally, other potential causes of long-term low $CD4^+$ T lymphocyte count (such as other types of immunodeficiency or immunosuppression, chronic viral infections, hematologic malignancies, long-term use of immunosuppressive drugs, etc.) must be excluded. The incidence of INR is between 10% and 40%. These patients have a significantly increased risk of opportunistic infections, malignant tumors, non-AIDS-defining events (NADE), and death.

10.2 Risk factors

The most clearly identified risk factors for INR are lower baseline $CD4^+$ T lymphocyte count and older age. Other

factors such as baseline viral load, WHO disease stage, and the timing of ART initiation may also have influence.

10.3 Clinical management

The most important measure to preventing the occurrence of INR is to initiate ART as early as possible. For patients with persistently low CD4+ T lymphocyte counts after long-term treatment, it is necessary to first re-evaluate the virological effectiveness of ART and exclude other potential diseases, drug factors, or testing interferences that may affect CD4+ T lymphocyte counts. Currently, there is no clearly effective treatment for INR. Clinically, regular monitoring is essential, and measures should be taken to prevent opportunistic infections and screen for NADE based on CD4+ T lymphocyte levels. For patients who have achieved virological suppression, adjustments to ART to improve immune reconstitution are not recommended.

Recommendation 34: Patients who have been on ART for more than 4 years, with peripheral blood viral load below the detection limit (<50 copies/mL) for over 3 years, and CD4+ T lymphocyte counts remaining below 350/μL, while excluding other potential causes for long-term low CD4+ T lymphocyte counts, should be considered as having INR (B1).

Recommendation 35: There is no clearly effective treatment for INR. Clinically, regular monitoring is essential, and measures should be taken to prevent opportunistic infections and screen for NADE based on CD4+ T lymphocyte counts. For patients who have achieved virological suppression, adjustments to ART to improve immune reconstitution are not recommended (B1).

11. AIDS-associated Neoplasms[23,50]

HIV-positive individuals have a higher risk of developing malignancies compared to the general population. Various factors contribute to this increased risk, including immunosuppression, the direct effects of HIV itself, co-infections with other oncogenic viruses (such as Epstein–Barr virus, human herpesvirus-8, human papillomavirus, HBV, and HCV), and environmental factors. AIDS-defining cancers primarily include non-Hodgkin lymphoma, Kaposi's sarcoma, and cervical cancer. HIV-positive women aged over 25 years are advised to undergo regular cervical cancer screening.[21]With the widespread use of ART and the extended life expectancy of HIV-positive individuals, the spectrum of cancers in these patients has changed. The incidence of AIDS-defining cancers has significantly decreased, and their proportion among the cancer burden in HIV-positive individuals is diminishing. However, the incidence of non-AIDS-defining cancers, such as Hodgkin lymphoma, liver cancer, lung cancer, and anal cancer, is increasing, necessitating screening, diagnosis, and management.[51] Malignancies in HIV-positive individuals often present with a younger age of onset, atypical pathological changes, more aggressive clinical behavior, and more advanced clinical stages at diagnosis. The diagnosis of these neoplasms relies on pathological biopsy. The general principles of treatment are similar to those for HIV-negative individuals, but the immunocompromised state of AIDS patients, often accompanied by opportunistic infections and other comorbidities, can affect treatment tolerance and efficacy, as well as increase the risk of infections. Personalized comprehensive treatment, including surgery, chemotherapy, targeted therapy, immune therapy, intervention therapy and radiotherapy, should be offered based on the patient's disease state (for more details, please refer to relevant guidelines). ART is recommended to be initiated as soon as possible for all AIDS patients with cancers. Drug–drug interactions between antiretroviral and anti-neoplastic medications need to be considered, and ART regimens with less bone marrow suppression and fewer drug–drug interactions should be selected where possible. The diagnosis and treatment standards for cancers should not be lowered due to HIV infection. Standardized diagnosis and treatment should be provided, and the use of a multi-disciplinary treatment (MDT) model is encouraged. Treatment plans should be developed in collaboration with experts from oncology, hematology, interventional radiology, pathology, surgery, and other relevant specialties. During treatment, special attention should be paid to preventing various complications, particularly infections.

Recommendation 36: During follow-up, HIV-positive individuals should be screened for both AIDS-defining cancers and non-AIDS-defining cancers. HIV-positive women aged over 25 years are advised to undergo regular cervical cancer screening (C1). All AIDS patients with cancers are recommended to initiate ART as early as possible, with careful consideration of the interactions between antiretroviral and anti-neoplastic drugs. ART regimens with minimal bone marrow suppression and drug–drug interactions should be selected. The use of a MDT model is encouraged to provide standardized diagnosis and treatment for HIV patients with cancer (C1).

12. Prevention of Mother-to-child HIV Transmission and Reproductive Options for HIV-serodiscordant Couples

Three principles need to be considered in the prevention of mother-to-child HIV transmission: (1) Lower the rate of mother-to-child transmission of HIV; (2) Improve the health and the survival rate of infants; and (3) Pay attention to the health of HIV-positive mother and their children. Effective specific interventions to reduce the risk of mother-to-child HIV transmission include the early administration of ARVs, obstetrical management, and counseling on postnatal feeding.

12.1 Prophylaxis with ARVs

All HIV-positive pregnant women should receive lifelong ART as soon as possible, regardless of their CD4+ T lymphocyte count or clinical staging.

The key points of implementing ART to prevent mother-to-child transmission of HIV are: (1) Initiate ART as early as possible after the pregnant woman is diagnosed with HIV during pregnancy, aiming to achieve virological suppression as quickly as possible. (2) Continue ART throughout the

pregnancy to maintain virological suppression. (3) Administer prophylactic antiretroviral treatment to newborns at different risk levels of HIV infection to further reduce the risk of perinatal mother-to-child transmission.

Preferred regimen: FTC/TDF (or TDF + 3TC) or FTC/TAF (or TAF + 3TC) or ABC/3TC (or ABC + 3TC) + DTG or RAL.

Alternative regimen: FTC/TDF FTC/TDF (or TDF + 3TC) or FTC/TAF (or TAF + 3TC) or ABC/3TC (or ABC + 3TC) or AZT/3TC (or AZT + 3TC) + EFV (or RPV or LPV/r); BIC/FTC/TAF.

Recommendation 37: All HIV-positive pregnant women should initiate lifelong ART as early as possible, regardless of their CD4$^+$ T lymphocyte count or clinical stage of disease (B1). The preferred ART regimen for pregnant women is a triple-therapy regimen that includes DTG or RAL (A1).

Antiviral treatment should be prophylactically administered to infants born to HIV-positive women as soon as possible (within 6 h after delivery), and specific dosing regimens should be determined based on the risk of exposure.[52] Children at average risk of exposure: for children of women on ART with a high level of adherence and long-term virological suppression, AZT or nevirapine (NVP) can be prophylactically administered for 4 weeks; NVP is preferred if breastfeeding is chosen. In children at high risk of exposure, a triple regimen of AZT + 3TC + NVP (or LPV/r) should be administered for 6 weeks after delivery to infants of women who have been on ART during pregnancy but have not achieved long-term virological suppression, women on less than 12 weeks of ART, or women found to be HIV-positive during delivery. AZT + 3TC + NVP is recommended in the first two weeks after delivery, while AZT + 3TC + LPV/r is recommended in weeks 2–6 after delivery. When conditions allow, AZT + 3TC + RAL can be used for 6 weeks after delivery.[53]

To prevent PCP, all infants born to HIV-positive women should receive PCP prophylaxis upon completion of 4–6 weeks of HIV prophylaxis, unless HIV infection has been ruled out.

Recommendation 38: Infants born to HIV-positive mothers should receive prophylactic antiretroviral medication as soon as possible after birth (within 6 h), with the regimen determined based on the level of exposure risk (B1).

12.2 Obstetrical management

Voluntary counseling on the prevention of mother-to-child HIV transmission and relevant testing should be provided to pregnant women with a confirmed diagnosis of HIV infection. The decision to terminate or to continue pregnancy should be made by pregnant women and her family after their informed consent is obtained.

For HIV-positive pregnant women who choose to terminate the pregnancy, prompt and safe surgical abortion should be performed to reduce the incidence of complications. For pregnant women who choose to continue the pregnancy, high-quality counseling on antenatal care and postpartum breastfeeding should be provided and appropriate interventions should be implemented.

HIV-positive pregnant women and their families should be provided adequate counseling and informed of the important role of institutional delivery in protecting maternal and child safety and preventing mother-to-child HIV transmission. Moreover, they should be offered assistance regarding an early confirmation of the delivery hospital and arrive at the designated hospital for delivery as soon as possible. HIV infection is not an indication for cesarean section. It is recommended to perform HIV RNA testing for pregnant women at 36 weeks of gestation or within 4 weeks of delivery. If the viral load is >1000 copies/mL or the viral load is unknown, a planned cesarean section at 38 weeks of gestation is advised to minimize the risk of perinatal HIV transmission.[23] Moreover, cesarean section is not recommended and urgent cesarean sections should be avoided in pregnant women who have been on ART during the first and second trimesters of pregnancy, pregnant women regularly taking medications, pregnant women who do not present with clinical symptoms of AIDS, women with viral loads <1000 copies/mL during the third trimester of pregnancy, and women approaching childbirth.[52] If there are other indications for a cesarean section, the procedure should be performed according to those indications. Current clinical research suggests that the duration of membrane rupture is not associated with the rate of mother-to-child HIV transmission. Therefore, membrane rupture should not be considered an indication for cesarean section to prevent HIV mother-to-child transmission.

Healthcare facilities should provide HIV-positive pregnant women with safe obstetric services and, when possible, avoid invasive operations that may increase the risk of mother-to-child HIV transmissions during delivery where possible (including lateral episiotomy, amniotomy, vacuum-assisted delivery with ventouse or forceps delivery, and intrauterine fetal scalp monitoring).

12.3 Postpartum breastfeeding guidance

Even with continuous ART and virological suppression during pregnancy and postpartum, absolute safety of breastfeeding cannot be ensured, and the risk of HIV transmission remains approximately 1%.[54,55] Formula feeding is recommended for children born to HIV-positive pregnant women. Breastfeeding should be avoided, and mixed feeding should be prohibited. Medical professionals should assess HIV-positive pregnant and postpartum women and their families regarding the acceptability, knowledge, and skills for scientific feeding, the cost burden, the ability to consistently obtain sufficient, nutritious, and safe breast milk substitutes; and the timely access to comprehensive counseling and support from medical professionals. When possible, guidance and support regarding formula feeding should be provided. For HIV-positive pregnant women who are not eligible for scientific feeding and, hence, choose breastfeeding,

adequate counseling on the correct practices of exclusive breastfeeding should be offered to these women and their families. ART must be sustained during the entire lactation period and breastfeeding preferably should not be continued beyond 6 months. Meanwhile, the children born to HIV-positive women should be provided services, including conventional healthcare services, child growth monitoring, monitoring of HIV infection, guidance on preventing malnutrition, vaccination, and HIV testing services (including antibody assays and early nucleic acid testing).

Recommendation 39: Infants born to HIV-positive mothers are recommended to be fed scientifically, avoiding breastfeeding and strictly prohibiting mixed feeding (A1). For HIV-positive mothers and their families who choose to breastfeed due to the lack of artificial feeding conditions, comprehensive counseling and informed consent should be provided. They should be guided to practice exclusive breastfeeding correctly and must adhere to ART throughout the entire breastfeeding period, which should not exceed 6 months (A1).

12.4 Follow-up of children born to HIV-positive women

HIV nucleic acid testing should be performed for the early diagnosis of HIV infection within 48 h after birth, as well as 6 weeks and 3 months after birth. HIV antibody assays should be performed 12 months and 18 months after birth.[52] HIV antibody tests should be repeated once 24 months after birth for HIV-exposed children who test positive for HIV antibody 18 months after birth and negative for HIV nucleic acid. To monitor the safety of administering medications for infection prophylaxis, routine blood and liver function tests should be performed after birth as a reference for baseline evaluation. The intervals of subsequent monitoring depend on the results of the baseline liver function and routine blood tests, gestational age, clinical status of the newborn infants, the dose of AZT or NVP, and the use of other drugs.

12.5 Reproductive options for HIV-serodiscordant couples

For consistently virally-suppressed HIV-positive women on ART with an HIV-negative male partner, natural conception during ovulation or *in vitro* fertilization are recommended. For consistently virally-suppressed HIV-positive men on ART with an HIV-negative female partner, natural conception during ovulation is also recommended as it is currently believed that no HIV transmission occurs between spouses under these circumstances.[53] Under certain circumstances, if the HIV-positive male partner attempts natural conception when viral suppression has not been achieved, the HIV-negative female partner should continuously take TDF/FTC (or TDF + 3TC) for exposure prophylaxis from 20 days before unprotected sexual intercourse during ovulation until 1 month after intercourse. If natural conception is attempted, the HIV-negative partner should be tested for HIV antibodies after unprotected sexual intercourse to prevent HIV transmission. It is generally recommended to test for HIV antibodies at 1 month and 3 months after unprotected sex.

Achieving persistent viral suppression in the HIV-positive partner on ART is the key to preparing for pregnancy in HIV-serodiscordant couples. In addition, the accurate calculation of the ovulation period is vital for improving the success rate of conception. Couples should seek professional help from a gynecologist if necessary.

In case of limited or no access to viral load testing, ART is recommended to be sustained for over 6 months before conception. In such instances, it is good practice to seek advice from an HIV specialist and the HIV-negative partner needs to take medications for exposure prophylaxis.

13. HIV Exposure Management and Prophylaxis[21,56–58]

13.1 PEP

PEP refers to a biological method of taking specific antiretrovirals as soon as possible (within 72 h) to reduce the risk of HIV infection after exposed to high risk of HIV infection (e.g. exchange of bodily fluids with HIV-positive people or people with unknown status).

HIV exposure is divided into occupational and non-occupational exposures.

13.1.1 Occupational exposure

HIV occupational exposure refers to the exposure to the blood, tissue, or other bodily fluids of HIV-positive people by healthcare workers, policemen, or other personnel at risk of HIV infection at work.

Routes of HIV exposure and their risk levels: (1) The routes of occupational exposure include contact with damaged skin (pricks or cuts, etc.) and contact with non-intact skin or mucous membranes. If the exposure source is the blood of HIV-positive people, the risks of acquiring HIV via exposure to damaged skin and mucous membrane are 0.3% and 0.09%, respectively. The risk of HIV infection via exposure to non-intact skin is still unclear but is generally considered to be <0.1%. (2) Grading of exposure risks: (a) low transmission risk: low viral load level, exposure source is on ART and has achieved persistent virological success; (b) high transmission risk: high viral load level, end-stage disease (AIDS), exposure source is not on or poorly adheres to ART; and (c) the unknown exposure source, lack of information on the disease stage and HIV status of the source, as well as the viral load of the contaminated medical devices or items.

Principles of occupational HIV post-exposure management: (1) Contaminated sites should be washed with liquid soap and running water. (2) Contaminated mucous membranes, such as conjunctiva, should be flushed repeatedly with a large amount of isotonic sodium chloride solution. (3) If a wound is involved, express contaminated blood from the lesion as much as possible by gently squeezing the wound from proximal towards distal pressure points, and

then rinse the wound with liquid soap and running water. (4) Local wound disinfection can be performed with 75% alcohol or 0.5% iodophor.

Principles of medication regimens for HIV prophylaxis after occupational exposure: (1) PEP regimens: The preferred and recommended PEP regimens are TDF/FTC (or FTC/TAF) + INSTIs (BIC or DTG or RAL). If INSTIs are not available, PIs, such as LPV/r and DRV/c, can be used. AZT/3TC can be used in individuals with decreased renal function and no HBV infection. A domestic study has shown that PEP regimen containing albuvirtide (albuvirtide + DTG, or albuvirtide + TDF + 3TC) has high treatment completion rate, compliance, and good safety, but more researches needed on this regimen.[59] (2) Timing of PEP initiation and recommended duration: PEP should be initiated as soon as possible after HIV exposure (within 2 h where possible). It is best to start PEP within 24 h after exposure, but no later than 72 h. PEP should be continuously administered for 28 days.

HIV monitoring after occupational exposure: HIV antibody testing should be performed immediately and at 4 weeks, 8 weeks, 12 weeks, and 24 weeks after occupational exposure to HIV. For HIV-exposed and HBV-positive individuals, HBV-related indicators should be monitored after the discontinuation of prophylaxis.

Prevention of occupational exposure: The measures to prevent occupational exposure mainly include standardized procedures and prophylaxis.

13.1.2 Non-occupational exposure to HIV

Non-occupational exposure to HIV refers to HIV exposure resulting from other personal behaviors besides occupations. The principles of non-occupational exposure evaluation and management, especially medications for prophylaxis, are the same as those for occupational exposure. In particular, prophylactic drug administration after exposure evaluation should be voluntary, and standardized follow-up procedures are needed to identify individuals infected with HIV as soon as possible. During baseline testing, the HIV status should be confirmed first for people with multiple histories of receiving PEP.

13.1.3 Precautions

(1) All PEPs should be administered voluntarily, and the informed consent form needs to be signed. Emphasis should be placed on adhering to standardized follow-up procedures. (2) Enquire in detail whether the individual has previously undergone PrEP/PEP. (3) Consider conducting pre-prophylaxis baseline tests, which include routine blood tests, assessments of liver and renal function, and tests for HBV infection status. (4) It is recommended to conduct HIV RNA testing before initiating prophylaxis, particularly for individuals who have a history of prior prevention attempts.

13.1.4 Post-exposure follow-up and monitoring

After starting PEP, conduct complete blood count, liver and renal function tests, and HIV antibody tests at 2 weeks, 4 weeks, and 12 weeks. If possible, perform HIV RNA testing as well. For individuals co-infected with HBV, monitor HBV DNA and other relevant indicators after discontinuing medication.

Recommendation 40: Before initiating HIV PEP, it is recommended to conduct HIV RNA testing, especially for individuals with a history of using prophylactic medications (A1). After HIV exposure, prophylactic medication should be administered as soon as possible (preferably within 2 h), ideally within 24 h, but no later than 72 h, and should be taken continuously for 28 days (C1). The preferred PEP regimen is FTC/TDF (or FTC/TAF) in combination with an INSTI (BIC, DTG, or RAL) (C1).

13.2 PrEP

PrEP is defined as a biological prophylactic method of lowering the risk of infection via antiretrovirals for individuals at high risk of HIV infection.

13.2.1 Target population

MSM, intravenous drug users, substance or alcohol abusers, sex workers, sexually active individuals (young adults and adolescents), and partners of people living with HIV.

13.2.2 Principles of drug administration

There are two main oral medication regimens for PrEP: the daily regimen and the event-driven regimen (event-driven PrEP [ED-PrEP]; also known as on-demand regimen).

Daily drug administration:[58] Daily oral PrEP with TDF/FTC (or FTC/TAF) is recommended for all populations at high risk for HIV infection.It is recommended to take one tablet of FTC/TDF (or FTC/TAF) orally every 24 h. If PrEP withdrawal or discontinuation is intended, PrEP should be continued for 7 days after the last exposure.

On-demand dosing (2-1-1 regimen): (1) 2-1-1 regimen: 2 tablets of TDF/FTC (or FTC/TAF) taken orally 2–24 h before expected sexual activity. After sexual exposure, 1 tablet should be taken 24 h after the last administration and another tablet should be taken 48 h after the first dosing. If high-risk sexual behavior occurs again before completing the on-demand regimen, continue taking one tablet daily until 48 h after the last sexual exposure. (2) CAB-LA is a long-acting intramuscular injection for PrEP. The recommended administration is an intramuscular injection of 600 mg in the gluteal muscle. The first two injections should be given 4 weeks apart, followed by an injection every 8 weeks. It is recommended for PrEP, particularly for individuals with renal insufficiency, poor adherence to oral PrEP regimens, or those who prefer a long-acting option.[6,23,58]

13.2.3 Follow-up visits and monitoring

Follow-ups and HIV antigen/antibody testing should be performed 1 month after PrEP initiation. Subsequently, follow-up visits are conducted once every 3 months. If possible, conduct HIV antibody and HIV RNA testing at each visit. Changes in liver and renal functions should be monitored. Testing for markers of HBV infection and syphilis serology testing are also recommended during each follow-up visit. HCV antibody tests should be performed annually.

13.2.4 Precautions

Baseline tests, standardized follow-ups, and behavioral assessments must be performed.

Recommendation 41: Before implementing PrEP, it is important to conduct an HIV exposure risk assessment and medical and suitability evaluation (C1). There are two oral PrEP regimens available: the daily regimen and the event-driven regimen, with medication options including FTC/TDF (or FTC/TAF) (A1). For those who cannot choose oral medication, the CAB-LA intramuscular injection regimen is an alternative (A1).

14. Whole-course Management of HIV Infection

The introduction and application of ART have significantly lowered the incidence of AIDS-related opportunistic infections and tumors, turning HIV infection into a chronic but manageable disease that is incurable at present. As the life expectancy increases, the incidence of a variety of non-AIDS-defining diseases (NADs), including metabolic syndrome, cardiovascular and cerebrovascular diseases, chronic liver, kidney, and bone diseases, and non-AIDS-defining tumors has also been increasing. These diseases have become the major factors affecting the quality of life and prognosis of patients with HIV infection/AIDS in the post-ART era.[21,23,60] Changes in the disease spectrum brought by ART are also changing the model of diagnosis, treatment, and care for HIV/AIDS patients. Whole-course management of HIV infection refers to a management model that facilitates comprehensive diagnosis, treatment, services, and care provided by a MDT throughout the entire course of treatment for HIV-positive patients. Whole-course management primarily focuses on: (1) Prevention and early diagnosis of HIV infection; (2) Diagnosis, treatment, and prophylaxis of opportunistic infections; (3) Initiation of personalized antiviral therapies, follow-ups, as well as education and monitoring of adherence; (4) Screening and management of NADs; (5) Comprehensive psychosocial care. The diagnosis and treatment model adopted in the whole-course management of HIV infection is characterized by multidisciplinary collaboration, led by infectious disease clinicians.

14.1 Prevention and early diagnosis of HIV infection

Counseling on the prophylaxis against HIV infection should be offered to high-risk populations, including guidance on safer sexual practices, the use of PrEP and PEP, prevention of mother-to-child transmission, and early ART initiation for patients with HIV/AIDS. Early testing and counseling on testing services (including nucleic acid testing) are recommended.

14.2 Opportunistic infection diagnosis, treatment, and prophylaxis

Please refer to "7. Opportunistic Infections". For patients diagnosed with late stage disease, especially those in the advanced stages of HIV infection (defined as having a $CD4^+$ T lymphocyte count <200/μL at diagnosis or at WHO clinical stage III/IV with AIDS-defining illnesses), special attention should be given to screening for various opportunistic infections. It is recommended to include tuberculosis and cryptococcosis screening as part of routine clinical practice.[61]

It is advised to systematically screen HIV-positive individuals for tuberculosis at each visit. In clinical practice, attention should be paid to the patient's history, typical symptoms and signs of tuberculosis, as well as imaging and laboratory tests, to systematically screen HIV patients for the possibility of tuberculosis.[17]

Early detection and treatment are crucial for improving the prognosis of patients with cryptococcal meningitis. It is recommended to conduct serum cryptococcal antigen (CrAg) screening for HIV-positive individuals with a $CD4^+$ T lymphocyte count <200/μL. Those who test positive should undergo cerebrospinal fluid examination to rule out cryptococcal meningitis.[21,29,62]

It is important to note that HIV/AIDS patients co-infected with SARS-CoV-2, Mpox, or other infections are at increased risk of severe disease, and emphasis should be placed on the prevention and treatment of these conditions.

14.3 Initiation and follow-up of individualized ART

Early initiation of ART is recommended for all individuals with HIV/AIDS regardless of their $CD4^+$ T lymphocyte counts. In clinical practice, ART regimens should be developed based on a comprehensive analysis of the patient's disease status, presence of complications including co-infections and tumors, underlying diseases, drug–drug interactions, patient adherence, viral load, HIV resistance (especially considering HIV resistance profile among local populations), accessibility, resistance barrier, and adverse effects (especially long-term adverse effects). Before initiating ART, it is recommended to conduct appropriate baseline testing and evaluations, include HIV RNA, $CD4^+$ T lymphocyte count, HIV resistance testing, complete blood count, urinalysis, liver and renal function tests, blood glucose, blood lipids, and screening for co-infections such as viral hepatitis, cryptococcosis, tuberculosis, and STIs.[5,37]

Special attention should be given to issues related to ART and follow-up in vulnerable populations. Vulnerable populations primarily include: patients over 50 years of age, pediatric patients, pregnant women, patients with late diagnosis, patients with multiple comorbidities, patients

with severe immunosuppression such as $CD4^+$ T lymphocyte counts <50/μL, and patients with incomplete immune reconstitution after ART. These patients should be more proactively engaged in ART, actively treat underlying conditions, and ensure multidisciplinary collaboration. For elderly patients, it is recommended to initiate ART as soon as possible (on the day of diagnosis or within 7 days of diagnosis). Screening for various chronic diseases such as diabetes and CVD should be conducted. Regular monitoring of bone density, liver and renal function, and neuro-cognitive function is advised. For elderly patients who are on multiple medications, it is important to simplify treatment regimens for chronic diseases and ART as much as possible to improve treatment adherence.[5,6]

Medication adherence is the most vital determinant of ART success; thus, patients must be well-educated on medication adherence before ART is initiated. During follow-up visits, long-term adverse drug reactions need to be monitored and ART regimens must be adjusted or measures taken accordingly. The case management model is recommended in standardized patient follow-ups and management.

In recent years, the concept of individualized ART has been proposed. Individualized ART, usually guided by TDM, which means to adjust the drug dosage based on blood drug concentrations. Although routine TDM is currently not recommended in clinical practice, TDM is recommended for: patients on regimens with clinically significant drug–drug interactions; patients with clinically significant liver and renal dysfunctions; patients experiencing dose-related adverse effects; patients undergoing changes in dosage; patients having good adherence to therapies but achieving poor ART efficacy; pregnant women who are on ART and at higher risk.

Adjustment of regimens is not recommended for patients showing effective viral suppression after ART. The optimization of ART regimens can be considered under the following circumstances. clinically, this is also referred to as safe transition of a regimen[5]: (1) Simplification of the medication regimen by reducing the number of tablets and dose frequency; (2) Improving drug tolerance by reducing short-term or long-term toxicity; (3) Preventing or alleviating drug–drug interactions; (4) Optimization of ART for pregnant women or patients who might become pregnant; (5) Reduction of treatment costs; (6) Switching to long-acting injectable formulations to reduce drug burden. Therapy optimization should be based on maintaining viral suppression to reduce adverse events and drug toxicity, improve patients' quality of life, and enhance long-term outcomes, without posing threats to the future selection of medications. When optimizing ART regimens, special attention should be paid to a patient history of HIV drug resistance and HBV or HCV co-infections. Patients with virological suppression and no history of transmissible or acquired HIV resistance can usually be switched to any preferred initial ART regimen while maintaining virological suppression. After adjusting the treatment regimen, it is important to monitor virological suppression and drug-related adverse effects. It is recommended to perform viral load testing and checks for adverse effects one month after the regimen adjustment.[6]

14.4 Screening and management of NADs

ART has turned HIV infection into a chronic disease that should be followed up and managed using models for chronic disease management. During follow-up visits, the evaluation and screening for NADs should be performed and prophylactic or treatment measures should be taken according to the evaluation results.[21] Routine clinical management practices for patients with HIV/AIDS who have not started ART should incorporate the screening and evaluation of CVD risk factors.[63] For patients with a high risk of CVD, it is recommended to choose INSTIs-based ART regimen and avoid regimens containing abacavir or LPV/r. For patients already on ART, follow-up should include careful assessment of CVD risk and the implementation of appropriate preventive interventions. Patients on INSTIs-based ART regimens should undergo annual diabetes screening and CVD risk assessment. For patients with high CVD risk, the ART regimen should be adjusted accordingly, and efforts should be made to actively control related CVD risk factors such as smoking cessation and control of blood glucose level, blood lipids level, obesity, and blood pressure.[21]

For patients with HIV infection with chronic illnesses, including hypertension, diabetes, dyslipidemia, atherosclerotic heart disease, cerebrovascular disease, non-AIDS-defining tumors (especially liver, lung, breast, prostate, and colorectal cancer, etc.), chronic obstructive pulmonary disease (COPD), non-alcoholic fatty liver disease (NAFLD), and osteopathies, chronic disease management should be applied as general population, and screening and prophylaxis should be performed according to relevant guidelines.[21,23] It is important to note that chronic disease prevention and intervention medications, such as statins and antihypertensive drugs, may interact with ARVs. Adjustments to the ART regimen, the relevant intervention medications, or their dosages should be made as needed, and adverse drug reactions should be closely monitored.

Patients on ART often experience weight gain, especially during the first year of treatment. Studies have shown that patients using ART regimens containing INSTIs and/or TAF exhibit more significant weight gain.[64] It is recommended to monitor weight and body mass index (BMI) at the initiation of ART and follow up every 6 months thereafter. For patients with less than a 10% increase in weight, it is not advised to change the ART regimen solely for this reason; instead, attention should be given to lifestyle adjustments such as exercise and dieting.

As the life expectancy increases, special attention must be given to the impact of aging on the care of HIV/AIDS patients. The assessment of geriatric syndromes should be incorporated into comprehensive HIV care.[65] Diagnosis and treatment should be carried out based on the characteristics of these chronic diseases and the requirements of tiered medical services, and patients should be encouraged to seek treatment at specialized outpatient clinics in general hospitals.

14.5 Comprehensive psychosocial care

Patients should be offered comprehensive care and services,[23] including screening for mental health, counseling on healthy lifestyles (e.g. smoking cessation), screening of STIs and management (For HIV-positive individuals who continue to engage in high-risk sexual behaviors, annual screening for infections caused by sexually transmitted pathogens such as HBV, HCV, and *Treponema pallidum* (syphilis) should be conducted, even if HIV RNA is suppressed long-term), family fertility counseling, screening for HIV-associated neurocognitive disorder, counseling on travel and health, and palliative care. These services should be provided based on relevant guidelines or standards. Efforts should be made to create various conditions that facilitate convenient access to diverse diagnostic and therapeutic services for HIV/AIDS patients, ensuring the sustainability of medical services.

Counseling on vaccinations for patients with HIV/AIDS should be considered. For patients who are negative for HBsAg and HBsAb should be vaccinated against HBV as soon as possible, regardless of their HBV core antibody status. While the vaccination success rate in populations with CD4$^+$ T lymphocyte counts <200/μL is lower than that in HIV-negative populations and HIV-positive persons with higher CD4$^+$ T lymphocyte counts, HBV vaccination is still recommended. Patients with HIV/AIDS infected with SARS-CoV-2 have a higher fatality rate due to a higher proportion of severe cases.[66] HIV/AIDS patients are advised to receive the SARS-CoV-2 vaccine.[6,67]

Recommendation 42: All HIV-positive individuals are recommended to be managed using the whole-course management model (C1).

Recommendation 43: For late-diagnosed HIV-positive individuals, especially those in the advanced stages of HIV infection, screening for various opportunistic infections should be conducted. Screening for tuberculosis and cryptococcosis should be part of routine clinical practice (A1).

Recommendation 44: It is recommended to conduct serum CrAg screening for HIV-positive individuals with a CD4$^+$ T lymphocyte count <200/μL. Those who test positive should undergo cerebrospinal fluid examination to rule out the possibility of cryptococcal meningitis (B1).

Recommendation 45: Before initiating ART, it is recommended to conduct baseline testing and evaluations, including HIV RNA, CD4$^+$ T lymphocyte count, HIV resistance testing, complete blood count, urinalysis, liver and renal function tests, blood glucose, blood lipids, and screening for co-infections such as viral hepatitis, cryptococcosis, tuberculosis, and STIs (C1).

Recommendation 46: Special attention should be given to issues related to ART and follow-up in vulnerable populations. Vulnerable groups primarily include elderly patients over 50 years old, pediatric patients, pregnant women, patients with multiple comorbidities, patients with severe immunosuppression such as CD4$^+$ T lymphocyte counts <50/μL, and patients with incomplete immune reconstitution after ART. These patients should be more proactively engaged in ART, actively treated for underlying conditions, and ensure multidisciplinary collaboration in diagnosis and treatment (C1).

Recommendation 47: For patients with effective viral suppression after ART, it is not recommended to change the treatment regimen. Optimization of treatment should be based on maintaining viral suppression without compromising future drug options. When optimizing ART regimens, special attention should be paid to the patient's previous HIV resistance and any co-infection with HBV or HCV (A1). HIV-positive individuals with virological suppression and no history of transmissible or acquired HIV resistance can usually switch to any preferred initial ART regimen while maintaining virological suppression (A1).

Recommendation 48: All HIV-positive individuals should regularly undergo CVD risk assessment, screening, and preventive interventions. For patients with high CVD risk, the ART regimen should be adjusted accordingly, and efforts should be made to actively control related CVD risk factors, such as smoking cessation, blood glucose, blood lipids, obesity, and blood pressure control (C1).

Recommendation 49: Efforts should be made to facilitate convenient access to various diagnostic and therapeutic services for HIV/AIDS patients and to ensure the sustainability of medical services (B1). HIV/AIDS patients should receive guidance on vaccination (C1).

Appendix

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Conflicts of Interest

None.

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