Commentary

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# Clinical guidelines for the diagnosis and treatment of HIV/AIDS in China: Their potential benefits and impact on public health

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**SUMMARY** Since the first edition of the guidelines for the diagnosis and treatment of AIDS was published in 2005, the AIDS Specialists Group of the Society of Infectious Diseases has updated the guidelines three more times to include more thorough, practical, standardized, and specific content. The latest edition (the 2021 version) has recently been updated in China in accordance with clinical practice nationwide and results of the latest research. Compared to the four previous editions, the 2021 edition references the latest information on the epidemiology of HIV, the prevention of HIV transmission, standardized lab diagnosis, and clinical management. First, the guidelines highlight the concept of "enhancing the combination of early intervention, prevention, and treatment". The guidelines specify more detailed clinical phases (three clinical stages), the clinical staging and progression of AIDS, and patient prognosis. The guidelines also specify diagnostic criteria – HIV antibodies, HIV RNA tests, CD4 cell counts, and the patient's epidemiological history – to use in conjunction with symptoms to confirm an HIV infection. In addition, the guidelines summarize more advanced HIV/AIDS research in China by describing the different circulating recombinant forms (CRFs) and unique recombinant forms (URFs) in Chinese patients, by summarizing the most prevalent strains in the Chinese population, and by comparing disease progression by route of transmission and by the CD4+T cell count. Lastly, this edition describes ways to optimize programs to prevent mother-to-child transmission, strategies for diagnosis and treatment of opportunistic infections, the aging patient population, and specialized ART treatment programs for different populations living with HIV. The guidelines should not only help to prolong the life of people living with HIV and improve their quality of life but also encourage successful collaboration between scientific researchers and physicians in the area of HIV.

***Keywords*** clinical guidelines, diagnosis, treatment, HIV/AIDS, public health

## 1. Introduction

As of 2020, 38 million people were living with HIV/AIDS (PLWH) and 1.5 million were newly infected worldwide. Twenty-six million patients, or 71% of all patients with AIDS, received antiretroviral therapy (ART), and 62% of new infections came from high-risk populations and their sexual partners (*1*). If the 188 countries worldwide were divided into 10 levels of prevalence based on the survival rate of AIDS, the rate of new infections per year, and the mortality rate per year, China would rank in the eighth level. Moreover, 75% of PLWH live in 15 countries, including China. By the end of October 2021, China (excluding Hong Kong, Macao, and Taiwan) had reported 1.14 million HIV infections. From January to October 2021, 111,000 AIDS cases were reported nationwide, 97% of which were sexually transmitted (*2*). Although Chinese AIDS prevention and control efforts have made considerable progress over the past nearly 30 years, AIDS prevention and control in China is clearly still facing challenges comparing to the prevalence of HIV elsewhere in the world and infection status elsewhere in the world (*3*).

To optimize HIV/AIDS diagnosis, treatment, and management, the AIDS Specialists Group of the Society of Infectious Diseases, Chinese Medical Association has continuously updated Chinese guidelines for the diagnosis and treatment of HIV/AIDS (Guidelines for China) (*4*). The guidelines are now in their fifth edition since the first edition was published in 2005. Chinese guidelines for the diagnosis and treatment of HIV/AIDS (2021 edition) were published In December 2021; the latest version is more comprehensive, practical, standardized, and advanced.

## 2. Background of the update

Due to the aging population with HIV/AIDS, the longer duration of treatment, changes in the types of ART drugs, and complex management of non-AIDS-related diseases (NAD), the clinical management of patients with AIDS poses considerable challenges. The guidelines need to be updated continuously in accordance with new findings from clinical trials, real-world studies, and clinical practice and new thinking about HIV prevention and comprehensive disease management.

## 3. Advantages of the update

### 3.1. Drafted in less time

In 2005, Chinese Medical Association organized experts to draft Chinese guidelines for the diagnosis and treatment of HIV/AIDS. China had just launched its national program for free ART and partially subsidized treatment of opportunistic infections at that time, and clinical practitioners experience and clinical data were lacked. Thus, the first edition of the guidelines was published in 2006 over the course of a year, mainly based on guidelines and literature from other countries. Since then, the guidelines were updated in 2011, 2015, and 2018 (*5-7*). As clinical and real-world studies have been conducted in China and a new generation of ART drugs has become more available and affordable, the AIDS and Hepatitis C Specialists Group of the Society of Infectious Diseases, Chinese Medical Association recently initiated steps to update the guidelines in April 2021 to include concepts like promoting pre-exposure prophylaxis (PrEP) and comprehensive disease management. Top experts and clinical practitioners in HIV/AIDS gathered and discussed those topics. In October 2021, a first draft was completed , and the final version of the guidelines was published. The update and revision process illustrates China's advances in combating HIV/AIDS and the continued and diligent efforts by researchers and clinical practitioners over the past few decades (*8*).

### 3.2. Drafted more thoroughly

The 2021 edition of the guidelines was drafted bytop domestic experts in epidemiology, lab management, perinatal transmission, and basic research. Therefore, information about the epidemiology of HIV, prevention of its transmission, standardized lab diagnosis, free ART and other treatments available nationally has been incorporated in the guidelines, making them more comprehensive.

### 3.3 More scientific evidence involved

The 2021 edition of the guidelines refers to results of relevant domestic research and evidence from clinical practice, including the Expert Consensus on HIV Pre-exposure Prophylaxis (PrEP) Drugs and the Expert Consensus on Diagnosis and Treatment of Patients with AIDS and Pneumocystis Pneumonia in China. The guidelines also comprehensively cite and refer to results of foreign research. Moreover, the guidelines also highlight HIV/AIDS prevention, clinical diagnosis, patient follow-up and management, ART, HIV, and management of opportunistic infections in light of clinical practice in China and views of personnel at different levels of the healthcare system.

## 4. Highlights

### 4.1. Source control and early intervention

(*i*) The guidelines put forward the concept of "enhancing the combination of early intervention, prevention, and treatment."
The chapter on epidemiology describes UNAIDS' 6 95% targets to end AIDS (*e.g.*, 95% of PLWH know their HIV status and 95% of PLWH who know their status initiate treatment) for the first time. For the first time, the chapter also mentions PrEP and post-exposure prophylaxis (PEP) for high-risk groups to reduce HIV transmission.

The guidelines further encourage and ask clinical practitioners to pay attention not only to the diagnosis and treatment of diseases but also to the actions and goals promoted by epidemiological and public policies. There are no leakage in prevention and treatment.

(*ii*) In the chapter on PrEP and PEP, treatment of occupational exposure, follow-up of non-occupational exposure, and treatment options are highlighted in light of actual needs in China. Moreover, the cohorts in which the safety and efficacy of innovative ART drugs for PEP in China are being tested are described for the first time. Further data shall be added once available.

The guidelines also describe the eligible population, initiation process, treatment regimens, precautions, and follow-up survey of PrEP in detail. This indicates that PrEP is being implemented and promoted as a public health policy in China. In addition, the significance of HIV RNA tests before and after taking drugs for PrEP is also highlighted for the first time. Patients must take drugs for PrEP for 7 more days after the last high-risk sexual behavior. These aspects align with the current public health policy to "enhance prevention and prophylaxis and enhance regular follow-up" in China in order to provide clinical support of reducing new HIV infections (*9*).

### 4.2. Standardized diagnostic criteria

In the chapter on clinical staging and diagnosis, the concept of and diagnostic criteria for HIV/AIDS are

clearly described. The stage of disease includes acute HIV infection (stage I), chronic HIV infection (stage II), and AIDS (stage III). The importance of a nucleic acid test (NAT) for diagnosis is highlighted throughout the guidelines.

The 2021 edition of the guidelines illustrates that HIV antibody and HIV RNA tests are used to confirm an HIV infection, the epidemiological history for the diagnosis of acute HIV infection and HIV in infants, CD4 cell counts and symptoms for disease staging, and AIDS-related symptoms for diagnosis and treatment of AIDS.

4.3. Advances in research on HIV/AIDS in China

In the chapter on pathogenesis, results from pathology and epidemiology studies conducted by Chinese researchers are widely cited. The different circulating recombinant forms (CRFs) and unique recombinant forms (URFs) in Chinese patients are described for the first time.

Molecular epidemiology data from China has also been published. According to the fourth National HIV Molecular Epidemiology Study in 2015, the most prevalent strain in China is CRF07_BC, CRF01_AE, CRF08_BC and subtype B.

Data indicate that the disease progresses faster in men who have sex with men (MSM) who are infected with HIV, with an average of 4.8 years' development before AIDS stage.

For the first time, the guidelines mention that adequate immune reconstitution is not achieved in 10-40% of patients with HIV/AIDS despite long-term virological suppression. These patients are referred to as "inadequate immunological responders" or "immunological non-responders." Compared to patients in whom adequate immune reconstitution has been achieved, the inadequate immunological responders have a higher risk of progression to AIDS and non-AIDS events and a higher mortality rate (*10*).

4.4. Optimized programs to prevent mother-to-child transmission based on circumstances in China and clinical studies Prevention of mother-to-child transmission and single-positive family fertility based on clinical study of China.

ART regimens for pregnant women have been updated based on findings from recent research. Dolutegravir (DTG) is included in the first-line regimen for ART in pregnant women and tenofovir alafenamide (TAF)/ emtricitabine (FTC) is included in the second-line regimen.

Neonatal risk assessment indicators are clearer and more readily assessed. Different ART regimens will be selected based on the level of risk of perinatal HIV transmission. A newborn with a high risk of perinatal HIV transmission will receive standard triple therapy.

Another update is specification of the timing forearly HIV tests in newborns with perinatal HIV exposure. For accurate diagnosis, the newborn must undergo an HIV NAT test within 48 hours and at 6 weeks and 3 months after birth. HIV antibody tests will be performed at 12 and 18 months after birth. Based on clinical practice and results of research in China, babies with HIV exposure who have negative NAT results and positive antibody test results will need to undergo another HIV antibody test 24 months after birth.

For the first time, the guidelines mention that when an HIV-positive man without virological suppression attempts to have sex without a condom to conceivean HIV-negative woman, should take tenofovir (TDF)/ FTC (or TDF + lamivudine [3TC]) continuously 20 days prior to the date of sexual behavior and for 1 month after for prophylaxis.

4.5. Significance of lab testing to guide effective ART

The 2021 edition of the guidelines highlights the benefits of viral load and HIV drug resistance testing in HIV diagnosis and ART initiation. The guidelines now highly recommend increasing the frequency of HIV viral load tests, they cite the reason for increasing the test frequency and for use of ultrasensitive HIV viral load testing, and they recommend reducing the frequency of CD4 tests. For the first time, the guidelines indicate that HIV drug resistance testing should be done before ART, regardless of the treatment regimen used.

4.6. Diagnosis and treatment of opportunistic infections and when to start ART

(*i*) The Xpert MTB/RIF and Xpert MTB/RIF Ultra molecular diagnosis tests are clearly recommended as initial diagnostic tests for diagnosis of HIV/tuberculosis (HIV/TB). The updated guidelines emphasize that ART must be started within 2 weeks of tuberculosis treatment, but does not include tuberculous meningitis and drug-resistant tuberculosis

RAL is no longer recommended as a preferred protocol for HIV/TB.

The most important update is the description of an HIV/TB diagnosis that does not rely on LTBI test results, consistent with the WHO guidelines for a prophylactic drug strategy for TB.

(*ii*) Primary prophylaxis for nontuberculous mycobacteria (NTM) is not recommended for patients with rapid initiation of ART.

(*iii*) A treatment for cryptococcal pneumonia was specifically updated, and a treatment for cryptococcal antisepsis has been recommended for the first time. In the consolidation stage for treatment of cryptococcal meningitis, the recommended dose of fluconazole was increased to 600-800mg/d, which was based on clinical

studies by and evidence from Chinese researchers.

4.7. A solution for China: ART

(*i*) In alignment with international guidelines, the Chinese guidelines now propose that rapid initiation of ART or same-day initiation of ART can be considered for eligible patients.

(*ii*) A regimen including integrase inhibitors (INSTI) is one of the main recommended regimens for ART;

(*iii*) Based on clinical practice and an expert consensus in China, dual therapy is cited as a first-line regimen;

(*iv*) The single-tablet regimen is listed as the preferred treatment option. At the same time, generic drugs developed in China, such as azvudine and ainuovirine, are included in the guidelines for the first time.

(*v*) The dose of efavirenz (EFV) is specified as 400 mg, while EFV should not be used for patients with a viral load greater than 500,000 copies/mL (*11*).

(*vi*) Suitable INSTIs should be used in first-line ART regimens for children.

(*vii*) Albuvirtide is recommended for certain patients under special circumstances, including those with drug resistance.

After the publication of the 2021 guidelines, experts on the Editorial Committee have recently start training other medical personnel around the country on those guidelines. Experts will teach, combine practice with theory, and travel to places with a high incidence of HIV/AIDS and patients receiving long-term treatment. Information in the guidelines will be emphasized, highlights of the update will be cited, and actual cases from local clinical practice will be discussed. This should provide ample opportunities for training of and discussions with primary physicians across the country.

In conclusion, the 2021 edition of the guidelines covers results of the latest domestic and foreign research, it focuses on the clinical benefits of standardized treatment in clinical practice, it proposes ART regimens more suitable for PLWH in China, and it promotes whole process management of HIV/AIDS. The guidelines include findings from research and clinical studies by Chinese researchers, and the guidelines are more suitable for Chinese patients. During the period of the 14$^{th}$ Five-Year Plan, research on multidisciplinary treatment of HIV/AIDS and on metabolic syndrome will be conducted as the guidelines are promoted and implemented. This research will combine clinical practice and clinical research to further explore advanced medical technologies such as functional cures and gene therapies. This will help to lower the incidence and mortality rate, prolong the life of PLWH, increase their survival rate, and improve patients' quality of life.

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