

Review

Research Progress in the Epidemiology of HIV/AIDS in China

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ABSTRACT

After thirty-two years since the first domestic outbreak of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) among injection drug users (IDUs) and almost two decades of comprehensive response efforts by the Chinese government, HIV/AIDS remains a major public health problem. The increasing burden of HIV/AIDS and comorbidities, the emergence of new HIV subtypes and/or circulating recombinant forms and drug mutations, the changing transmission networks, and the urgency of immediate antiretroviral therapy initiation upon an HIV diagnosis are increasingly challenging and altogether likely to have significant impact on the HIV epidemic in China. Upon the call for the global AIDS response to end AIDS by 2030, China needs to develop an innovative and pragmatic roadmap to address these challenges. This review is intended to provide a succinct overview of what China has done in efforts to achieve the global goal of ending AIDS by 2030 and the recently proposed “95-95-95” target (95% combination prevention, 95% detection, 95% treatment, 95% viral suppression), and to summarize the most recent progresses in the epidemiological research of HIV/AIDS in China with the aim of providing insights on the next generation of HIV control and prevention approaches and to shed light on upgrading the national strategy to end AIDS in this country.

INTRODUCTION

As the global AIDS response shifts to end AIDS by 2030 upon a call from the new United Nations General Assembly Political Declaration, the Chinese effort to end AIDS is entering a new era. After thirty-two years since the first domestic outbreak of human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) among injection drug users (IDUs) and almost two decades of well-funded and comprehensive response efforts by the Chinese government, HIV/AIDS remains a major public health

problem and a major cause of deaths in China. At the end of 2020, there were 1.053 million people living with HIV (PLWH) and 351,000 cumulative reported deaths in China (1). The proportion of heterosexual and homosexual transmission increased from 48.3% and 9.1% in 2009 to 74.2% and 23.3% in 2020, respectively, whereas the proportion of HIV transmission by IDU declined substantially from 25.2% in 2009 to <2.5% in 2020. The standardized mortality of HIV/AIDS in China rose dramatically from 0.33 per 100,000 people in 1990 to 2.50 per 100,000 people in 2016 (2). The changing epidemiological profile and increasing burden of morbidities and mortalities, together with the emergence of new HIV subtypes and/or circulating recombinant forms (CRFs) and drug mutations, the changing transmission networks, and the urgency of immediate antiretroviral therapy (ART) upon HIV diagnosis are emerging challenges and threats and altogether likely to have significant impact on the HIV epidemic in China. We herein briefly review and summarize the most recent progresses in the epidemiological research of HIV/AIDS in China with an aim to shed light on upgrading the national strategy to end AIDS in this country.

COMBINATION PREVENTION

HIV Risks and Prevention in MSM

Men who have sex with men (MSM) are the highest-risk group for HIV infection and present an increasing public health challenge in China. Dong et al. estimated the national prevalence of HIV among MSM through a systematic analysis of data extracted from 355 studies (571,328 individuals) covering 59 cities from 30 provincial-level administrative divisions (PLADs) of China (3). The overall national prevalence of HIV among MSM from 2001 to 2018 was estimated to be 5.7% [95% confidence interval (CI): 5.4%–6.1%], with the highest in those aged 50 years or older (19.3%). HIV was highly prevalent among those with illiteracy (16.8%), those in the southwest

(10.7%), and those seeking partners in bathhouses/saunas (13.4%). The HIV incidence among MSM was around 5.0 per 100 person-years (PY) (4), varying from 3.5 to >10.0 per 100 PY (5–9).

Some innovative interventions, including electronic or internet-based technologies, crowd-sourcing, preexposure prophylaxis (PrEP), and postexposure prophylaxis (PEP), have recently been evaluated among MSM (10–12). Yun et al. conducted a randomized controlled trial (RCT) showing that mobile phone interventions based on an HIV risk prediction tool is promising in promoting HIV testing and reducing high-risk behavior among MSM (13). The same group also demonstrated that an assisted partner notification (PN) strategy could increase uptake of HIV testing among sexual partners of recently diagnosed MSM (14). Tang et al. demonstrated that an innovative crowdsourcing approach was effective for developing and strengthening community-based HIV testing services for MSM (15). Integrating social media with the distribution of self-test kits also holds promise to increase HIV testing coverage and case identification among MSM (16).

The national pilot PrEP and PEP program was first launched in Tianjin Municipality in 2017, and expanded to 7 PLADs by 2019. However, less than one thousand were regularly taking PEP and even fewer taking PrEP. The awareness of and willingness to use PrEP and PEP among MSM was still extremely low (17–18). The probable barriers were the high price of PrEP (69.9%), the need to use condoms consistently (52.7%), concerns about side effects (39.8%), and concerns about effectiveness of prevention (22.6%) (18). Adequate PrEP promotions should be implemented, especially on the internet and dating apps.

HIV Risks and Prevention in Older Men

Older men have been increasingly and disproportionately affected by HIV over the past decade in China (19–20). According to China National Center for AIDS/STD Control and Prevention (NCAIDS), the proportion of newly reported HIV-positive cases made by males aged 60 years or older increased from 7.41% in 2010 to 18.21% in 2020 (1). The majority of them were infected through heterosexual contact (21). A recent meta-analysis pooling 30 studies of older men that were mostly at high-risk or MSM conducted during 2010–2018 in 13 PLADs found that the pooled HIV prevalence in

people aged over 50 years was 1.68% (95% CI: 1.00%–2.79%), higher (2.60%) in eastern China than in central and western China (0.16% and 2.13%) (22).

Limited studies have been designed to examine new interventions for HIV among older adults. Only few studies have been conducted to explore the efficacy of internet-or-network-based measures such as crowdsourcing or mobile apps in promotion of safer sex or HIV testing among MSM including those older than 50 years (15). Given the increasing spread of HIV among them, more HIV intervention studies that are psychosocially tailored for older adults are called for.

HIV Risks and Prevention in College Students

Cai et al. characterized the newly reported HIV/AIDS cases in young students in China between 2010 and 2019 (23). A total of 23,307 HIV/AIDS cases were reported in young students, with an overall male to female ratio of 33.9:1 and a mean age of (19.90±2.05) years. The new diagnosis rate showed decreasing trends [annual percentage change (APC) =−17.0] in the age group 23–24 years but increasing trend in the age group 15–17 years from 2015 to 2019 (23). The transmission route was mainly homosexual contact for males and heterosexual contact for females. Male cases were mainly identified by voluntary counseling and testing (VCT) clinics, whereas female cases were mainly found in hospitals (24). Liang et al. showed that there was a huge gap between female university students' willingness and practice of accepting VCT, as only 2.16% of the participants have ever had HIV tests (24).

Promoting safer sex and awareness of HIV status among college students is a major challenge for HIV control in China. Jiang et al. implemented an anonymous vending machine-based urine self-collection for HIV testing (USCT) program in colleges across China (25). From June 2016 to December 2019, 146 vending machines stocked with urine self-collection kits were distributed on 73 college campuses across 11 PLADs. Among the total of 5,178 kits sold, 3,109 (60%) samples were returned, 2,933 (94%) were eligible for testing, and of them 2.3% were tested HIV-positive, indicating that USCT is a powerful complement to current interventions that target at-risk students and promote HIV testing. Furthermore, given the low acceptance of PrEP and PEP by college students (26), studies are warranted to address this challenge.

HIV Risks and Prevention in FSWs

Zhang et al. recently summarized the national and regional levels of HIV prevalence among female sex workers (FSWs) based on reported rates in the literature from 2008 to 2018 (27). The overall national HIV prevalence was below 1%, showing a sporadic pattern in most PLADs. However, in the PLADs of Yunnan and Guangxi, the median-reported prevalence rates were close to or slightly above 1% (27). Using BED-CEIA, the HIV incidence among FSWs in Sichuan Province was estimated to be 0.22% (95% CI: 0.16%–0.28%) during 2011 to 2015 (28). Unfortunately, an accurate depiction of the epidemic in this population was obscured due to the lack of data on incidence. Notably, a rise in illicit use of synthetic drugs and changing sexual practices may represent newer risk factors for HIV transmission among FSWs, and a coordinated risk reduction framework remains urgently needed to address the dual epidemics of drug use and sexually transmitted infections (STIs) (29).

National prevention programs for HIV prevention in FSWs have widely promoted male condoms as a primary and practical measure. Limited studies have examined the feasibility and efficacy of innovative prevention tools or strategies, such as female condoms, PrEP, and PEP, to prevent HIV among FSWs or male clients (30). Given the vulnerability of FSWs to HIV infection, more research to gain comprehensive understanding of HIV incidence, risk trends, and innovative intervention strategies is needed.

HIV Risks and Prevention in Other Key Populations

ART adherence by the HIV-positive spouses could substantially reduce secondary HIV transmission within serodiscordant couples (31–32). The coverage of ART for serodiscordant couples has increased from 58.1% in 2011 to 96.6% in 2020, and correspondingly, the HIV seroconversion rate among HIV-negative spouses has decreased from 2.60% in 2011 to 0.34% in 2020 (1). There is no doubt that immediate ART coupled with condom use for newly diagnosed HIV-positive spouses continues to be the most efficient strategy for preventing the HIV secondary transmission between serodiscordant couples.

Methadone maintenance treatment (MMT) has significantly reduced new HIV infections among IDUs in China. At the end of 2020, there were 791 MMT clinics and 22 mobile vans providing on-site MMT

across 29 PLADs where 91,000 patients were served (1). The HIV seroconversion rate has declined by fourteen-fold from approximately 1% in 2006 to 0.07% in 2020. Needle exchange program for IDUs is also ongoing in 12 PLADs.

HIV DETECTION

Promoting HIV testing was an essential method to achieve the first 90% of the global “90-90-90” target (90% detection, 90% treatment, 90% viral suppression) by 2020, and the second 95% of the upgraded global “95-95-95-95” target (95% combination prevention, 95% detection, 95% treatment, 95% viral suppression). The overall person-times of HIV testing increased over four-fold from 55.6 million in 2009 to >240 million in 2020 (1). This goal was achieved by rigorous efforts in massive HIV screening and testing strategies in the past decade. For example, VCT has rapidly scaled up, from 6,077 VCT sites identifying 19,611 HIV positives out of 1,679,654 attendants in 2008 to 11,319 sites identifying 28,498 HIV positives out of 2,832,985 attendants in 2020 (1). On the other hand, HIV testing in medical institutes has been largely promoted through opt-out testing for clinical patients. In 2020, approximately 188 million person-times were tested and 79,475 were tested positive for HIV (1). However, delayed diagnosis of HIV infection remains a major concern for this strategy. Recent studies investigated the feasibility of and effective ways to promote home-based HIV self-testing (HIVST) in key populations especially MSM in China. Yan et al. conducted a large-scale longitudinal study among MSM who received the HIVST service based on a mobile app providing the “Mail-in rapid test reagent kit” in Harbin, Heilongjiang Province from July 2017 to June 2018 (33). Overall, 10% of the MSM adhered to HIVST every 100 days. Twenty HIV seroconversions were observed during one-year follow up (34). Those who adhered to HIV testing were more likely to improve condom use behaviors, but these results were not statistically significant. Zhang et al. found that providing free HIVST kits significantly increased testing frequency among Chinese MSM and further effectively enhanced partner HIV testing through distribution of kits within their sexual networks (33). From 2015 to 2020, the number of HIVST kits sold on internet increased from 1 million to over 5 million (35). Future research is needed to provide more insights into the development of internet-based and/or

social/sexual network-based interventions for HIVST among key populations.

MOLECULAR EPIDEMIOLOGY

HIV-1 Subtypes and Recombinant Forms

The distribution of HIV-1 subtypes and CRFs was highly diverse and complex in China. Yuan et al. conducted a systematic review and meta-analysis to provide a comprehensive prevalence estimate of different HIV-1 subtypes in sexual transmission by 2016 in China (36). A total of 130 eligible studies were identified, including 18,752 successfully genotyped samples. The pooled prevalence of CRF01_AE, subtype B, CRF07_BC, CRF08_BC, and subtype C were 44.54%, 18.31%, 16.45%, 2.55%, and 0.37%, respectively. HIV-1 subtype distribution varied significantly between regions. Recently, Wang et al. analyzed all Chinese *pol* region (2,253–3,252) sequences in the HIV Database to evaluate potential new CRFs in China (37). They found that CRF01_AE was the most prevalent genetic form in China, accounting for 39.69% of all national infections, followed by CRF07_BC (20.47%), subtype B (17.50%), CRF08_BC (6.60%), subtype C (6.28%), CRF55_01B (2.06%), and other CRFs (1.77%). The unique recombinant forms (URFs) were responsible for 5.31% of all infections nationwide. Among URFs, genomes comprising BC, 01BC, 01B, and 01C were dominant. Song et al. demonstrated that the HIV-1 phenotype and pathogenicity can be determined at the phylogenetic cluster level in the same subtype, highlighting the importance of monitoring the genetic evolution and phenotypic shift of HIV-1 to provide early warning of the appearance of more pathogenic strains (38).

HIV Drug Resistance

High prevalence of HIV drug resistance (HIVDR) would restrict therapy options, compromise the effect of current therapy regimens, and increase the risk of treatment failure. Zuo et al. systematically reviewed and assembled 218 datasets from 170 studies between January 2001 and March 2019, covering 21,451 ART-naive and 30,475 ART-treated PLWH in China (39). The pooled prevalence of transmitted drug resistance (TDR) was 3.0%, including 0.7%, 1.4%, and 0.5% resistance for nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and

protease inhibitor (PIs), respectively. TDR in the country overall has risen since 2012, and this rise was driven mainly by NNRTI resistance. Also, 1 NRTI-associated (M184V/I) and 3 NNRTI-associated (K103N/S, Y181C/I and G190A/S) mutations had high percentages in ART-naive and ART-treated individuals, and these mutations conferred high-level resistance to 3TC, EFV, and/or NVP (39).

HIVDR or mutations to PIs and other antiretroviral drugs (ARV) were also emerging. Yang et al. investigated the prevalence of integrase strand transfer inhibitors (INSTI)-associated resistance of HIV-1 strains in Henan Province during 2018–2020 (40). The prevalence of INSTI resistance was 1.2% overall, 0.63% for ART-naive patients, 2.05% for ART-treated patients with 14.63% for INSTI-treated and 0.76% for INSTI-naive patients. In a study of HIV-1 gp41 genetic diversity and enfuvirtide (ENF/T-20) drug resistance-associated mutations (DRMs) among enfuvirtide-naive patients in southern China, known DRMs were detected in 27.5% of ENF treatment-naive patients, which have been proved to elevate resistance to ENF (41). Undoubtedly, HIVDR or DRMs will continue to evolve in an increasing trend which warrants enhanced surveillance and monitoring.

HIV Molecular Transmission Networks

In recent years, molecular transmission networks based on evolutionary theory and sequence analysis have been widely used in research on HIV transmission dynamics and for precise interventions for high-risk populations. Ma et al. conducted a study of PLWH who were sexually transmitted in Liaoning Province from 2003 to 2019 (42). They found that the molecular transmission networks formed by CRF01_AE, CRF07_BC, and B did not have interconnections. A molecular epidemiological study of HIV-1 among newly diagnosed MSM in 2017 in Jiangsu Province found that 182 (23.7%) of 767 sequences were included in the HIV-1 transmission networks, forming 79 clusters with 4 clusters identified as fast-growing (43). Transmission among young MSM within networks was greater than the other age groups; thus, they could be essential in the control of the HIV epidemic in Jiangsu Province. Li et al. constructed genetic transmission networks of CRF08_BC based on its *pol* sequences, derived from the National HIV Molecular Epidemiology Survey (44). Of the 1,829 subjects, 639 (34.9%) were clustered in 151 transmission networks. The most crossover links were found between heterosexual

women and IDUs, with 30.9% heterosexual women linked to IDUs. These new findings underscored the importance of constructing molecular transmission networks and conducting long-term molecular monitoring, in addition to constructing behavioral networks and contact tracing (45) to further inform targeted measures for precise HIV prevention and control.

ANTIRETROVIRAL THERAPY AND VIRAL SUPPRESSION

Presently, the 4th edition of the *China's National Guidelines for Free ART* serves as the standard national reference, with continuous updates in regimens, enrollment criteria for ART, monitoring for CD4 counts, and HIV viral load and adverse effects of ARV. At the end of 2020, 978,138 (92.9%) out of the total of 1.053 million PLWH in China were receiving ART, 96.1% of those on ART were able to achieve viral suppression (1). To further address the challenges in maintenance of a sustainable national ART program and a continuum of HIV care, including implementation of the test-and-immediately-treat policy and provision of care for individualized health needs of the patients (46–47), China is examining various service models for treatment and care. For example, the previous CDC-led AIDS treatment program and mode of management had been transferred to the hospital-based model years ago, which had proved to be effective and successful (48). Most recently, as the body of PLWH continuously increases, a community-based model for patient management is being examined to ameliorate work overload suffered in the hospital-based model.

BURDEN OF HIV/AIDS MORBIDITY AND MORTALITY

With a secondary analysis of the Global Burden of Diseases, Injuries, and Risk Factors Study 2017 data, Liu et al. observed that the HIV prevalence in China increased from 1990 to 2009 with an annual percent change (APC) of 10.7, and then remained stable from 2009 to 2017 (APC: 0.7) (49). A significant increase in HIV incidence was also observed for 1990 to 2005 (APC: 13.0) and then a significant decrease was detected for 2005 to 2017 (APC: –6.5). However, the AIDS-related mortality has increased sharply for 1990 to 2004 (APC: 10.3) and for 2013 to 2017 (APC:

15.3), although it stabilized for 2004 to 2013 (APC: 1.3) (49).

Morbidity and mortality of non-AIDS-defining diseases (NADs) have become the increasing burden of PLWH with long-term ART (50–57). Wang et al. carried out an evaluation of the burden, risk factors, and prognosis of serious non-AIDS-defining events (NADEs) among ART-naïve AIDS patients admitted to a tertiary hospital between 2009 and 2018 in China (58). Among 1,309 patients, 143 (10.9%) had at least one serious NADEs, including 49 (3.8%) with cerebrovascular diseases, 37 (2.8%) with non-AIDS-defining cancers, 28 (2.1%) with chronic kidney diseases, 26 (2.0%) with cardiovascular diseases (CVD), and 18 (1.4%) with liver cirrhosis. Liu et al. also quantified the contribution of modifiable risk factors to NADs including CVD, end-stage liver disease (ESLD), advanced renal disease (ARD), and non-AIDS-defining cancers (NADCs) among 8,301 PLWHs starting ART at the Third People's Hospital of Shenzhen (China) from 2010 to 2017 (59). Incidence of CVD (362 per 100,000 PY) was the highest among outcomes, followed by that of ARD (270 per 100,000 PY), ESLD (213 per 100,000 PY), and NADC (152 per 100,000 PY). The contribution of traditional risk factors such as smoking, hypertension, and diabetes for these NADs far outweighed the HIV-related risk factors. An earlier cross-sectional study found that a third of PLWH had metabolic associated fatty liver disease, formerly named non-alcoholic fatty liver disease (60). Individual-level interventions and population-level policymaking is needed to prevent NADs in long-term management of HIV infection in China.

SYSTEMS EPIDEMIOLOGY OF HIV/AIDS

Despite viral suppression by ART, HIV infection is associated with ongoing activation of the immune system and persistent inflammation (61), which are key driving forces in the loss of CD4+ T cells, progression to AIDS, and development of non-HIV-related but aging-related chronic complications (61). An early loss of gut mucosal integrity, the following microbial translocation, and other co-infections are all factors contributing to the ongoing immune activation and sustained inflammation (62). Genetic factors also play important roles in development of various non-communicable chronic diseases (NCDs) in HIV

infection. Zhao et al. demonstrated that the Asian-specific mitochondrial DNA haplogroups G and N9 may confer higher risk for the development of multiple sclerosis (MS) in PLWH in China (63).

Very recently, Ding et al. conducted a case-control study using untargeted metabolomics to characterize the key metabolites and metabolic pathways associated with HIV infection and multiple NCDs, focusing on identifying the common metabolic pathways underlying them (64). They found that PLWH presented widespread alterations in cellular metabolism versus HIV-negative individuals, and glycerophospholipid metabolism emerged as the potential common metabolic pathway underlying NCDs in treated HIV infection; followed by d-glutamine and d-glutamate, and alanine, aspartate and glutamate metabolism. The same group also performed 16S rRNA gene sequencing and untargeted metabolomics on fecal samples of PLWH with or without neurocognitive impairment (NCI). The results show that the decreased abundance of butyrate-producing bacteria, the increased abundance of *Klebsiella*, and the associated metabolites were associated with NCI in PLWH (65).

Further systems epidemiological research combining epidemiological data with system biology is needed to confirm these findings and to identify new mechanisms of aging-related NCDs comorbid with HIV infection using longitudinal multi-omics in China.

HIV/AIDS DURING THE COVID-19 EPIDEMIC

The coronavirus disease 2019 (COVID-19) pandemic has posed a serious threat to prevention, treatment, and healthcare services for HIV. From January 1 to April 16, 2020, 35 (0.58%) of 6,001 PLWH experienced COVID-19 in Wuhan city, and 197 (3.3%) had discontinued ART despite tremendous supportive efforts from both governmental and non-governmental organizations (66). In Jiangsu Province, the HIV testing rates decreased by 49.0% (919,938) in the first three months of implementing COVID-19 measures (67). Of an estimated 1,555 new HIV diagnoses expected in the same period, only 63.0% new diagnoses were recorded (67). Links to HIV healthcare services including CD4 testing and ART were also seriously affected (67). Alternative or substitute ways to access healthcare for HIV during the COVID-19 epidemic might be considered. For example, Jiang et al. found that more MSM self-tested

for HIV (52.1% *vs.* 41.6%) but fewer MSM used facility-based HIV testing (42.9% *vs.* 54.1%) during COVID-19 measures compared to before COVID-19 measures (68). Furthermore, as compared to PLWH in other countries and the general population in most parts of the world, PLWH in China reported a relatively low willingness to receive the COVID-19 vaccination (69). The internet and social media as well as interpersonal communications may be major sources of influence on PLWH's perceptions and willingness to receive COVID-19 vaccination, which have important implications for immunization programs targeting PLWH.

SUMMARY

Despite aggressive and proactive national anti-HIV/AIDS strategies and action plans, the number of newly identified HIV infections, diagnostic delays, HIV risks among key populations such as MSM and their sexual partners continues to rise in China. Innovative HIV interventions such as PrEP and PEP as well as intervention delivery utilizing information technology are increasingly examined and motivated, but lessons learned are less than encouraging. Without a deeper understanding of macrosocial epidemiology of HIV, scaling up HIV testing and treatment will be a necessary but insufficient strategy to end the epidemic. Aged- and culturally-appropriate health education, coupled with social prevention strategies, need to be a high priority among China's national HIV prevention priorities. Meanwhile, current facility-based HIV services should also be complimented by community-led services and including key populations as central to their responses, which requires much more implementation research.

With HIV infection as a chronic disease and NCDs as leading causes of death, efforts on screening, prevention, and management of comorbid NCDs are now warranted. It is also necessary to re-focus some of the research agendas and/or priorities in China. Systems epidemiological research integrating multi-omics technologies could inform new biomarkers and biomedical targets for HIV prevention and treatment. Furthermore, PLWH are at increasingly and disproportionately higher risks of psychoactive stress and sleeping and mental health problems, so intervention programs to decrease perceived stress should be developed and implemented in China's resource-limited mental health settings. Moreover, as the COVID-19 pandemic continues to spread around the

world, it is particularly important to ensure PLWH have equal access to the utilization of health education, interventions, and services for COVID-19 as well as other diseases including HIV/AIDS.

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