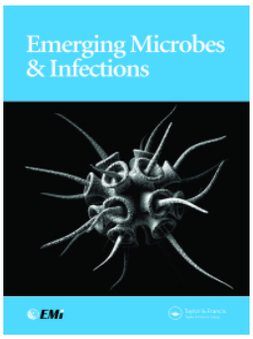

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Grand Challenges on HIV/AIDS in China – The 5th Symposium, Yunnan 2024

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ABSTRACT

HIV-1 infection has led to 1.329 million people living with the virus and 0.474 millions of deaths by the middle of 2024 in China. Achieving the goal of ending HIV/AIDS in China by 2030 has faced several grand challenges including currently having a diagnostic rate of less than 85%, an estimated annual cost burden of 6.3 billion RMB for antiretroviral therapy (ART) alone, and the lack of therapeutic cure and preventive vaccine and so on. To address these challenges, Chinese scientists initiated the programme of *Grand Challenges on HIV/AIDS in China* (GCC) in 2017. The inauguration symposium was held from 30 November to 1 December 2017 in Hong Kong – Asia's World City – to commemorate the 10th anniversary of AIDS Institute at The University of Hong Kong and Comprehensive AIDS Research Center at Tsinghua University. The mission of the GCC is to advance HIV/AIDS prevention, prioritize research on therapeutic cure and vaccine, disseminate new scientific findings, and foster broader collaborations. Following the inaugural event, subsequent symposia were held at Fudan University in 2018, Sun Yat-Sen University in 2019, Tsinghua University in 2023, and Dali University in 2024. This review reports the scientific presentations and progresses made by the GCC scientists, highlighting efforts to combat HIV/AIDS in China.

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KEYWORDS HIV-1; AIDS; cure; vaccine; China

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Introduction

The 5th symposium of *Grand Challenges on HIV/AIDS in China* (GCC) was successfully held on December 14-15, 2024 at Dali University in Yunnan, a southwestern province of China. Yunnan holds historical significance in China's HIV-1 epidemic, as it is where the first outbreak was identified in 1989 among a group of 146 intravenous drug users (IDUs) in the border city of Ruili, located in the Dehong prefecture bordering Myanmar [1,2]. The province has a long history of illegal opium and heroin trafficking, with the majority of these drugs in China historically trafficked through Yunnan from the "Golden Triangle" region of Southeast Asia – comprising northeastern Myanmar, northwestern Thailand, and northern Laos – where illicit drug production is concentrated. HIV-1 strains initially identified among IDUs in Yunnan became the source of a nationwide epidemic. The dominant C/CRF07/08_BC strains in Yunnan were the products of inter-subtype recombinants of those subtype B circulating in Thailand and subtype C in India, and they are genetically linked to viruses found among IDUs in neighbouring Guangxi province and the distant northwestern Xinjiang province, highlighting the role of drug-trafficking routes in viral dissemination [2,3]. The subsequent emergence and spread of CRF01_AE, then a dominant strain circulating in Thailand, fuelled a major expansion HIV-1 transmissions via sexual contact, particularly among men who have sex with men (MSM) and heterosexual females across Yunnan's 16 prefectures and subsequently throughout the whole country [4]. Although the subtype B (Thai B) was less prevalent in Yunnan, it caused a significant outbreak among paid blood donors (PBD) in Henan and adjacent provinces in central China during the 1990s, the exact transmission route and mechanism are currently unclear [5]. Historically, Yunnan was the province with the highest number of HIV-1 infections in China for many years. Yunnan's efforts to control the HIV-1 epidemic have served as a model for national strategies aimed at ending AIDS. The province has benefited from both national and international support to build an extensive network of integrated prevention programmes including condom promotion for sex workers, drug rehabilitation services, needle exchange programmes, and methadone maintenance therapy for IDUs, and most importantly free ART for all people living with HIV/AIDS (PLWHA). By the end of 2020, the number of PLWHA in Yunnan was approximately 127,000 [6]. The province is no longer ranked first in China by now for HIV-1 prevalence, having been surpassed by Sichuan, Guangxi and Chongqing.

The decision to hold the fifth symposium of *Grand Challenges on HIV/AIDS* in Yunnan carries strategic significance. It underscores the importance of promoting the nationwide implementation of the 95-95-95 strategy, a global initiative aiming to diagnose 95% of PLWHA, provide ART to 95% of those diagnosed, and achieve viral suppression in 95% of those receiving treatment, with the ultimate goal of ending AIDS in China by 2030 (Table 1).

Keynote speeches of the 5th Symposium of *Grand Challenges on HIV/AIDS in China*

Fusheng Wang highlighted recent global advances in ART-free HIV-1 virological control by discussing the eight cure cases achieved through bone marrow transplantation. He also reviewed progress in strategies such as the "shock and kill" approach, clustered regularly interspaced short palindromic repeats (CRISPR)-based HIV gene-editing, CAR-T therapy, anti-PD-1 treatment, therapeutic vaccination, and neutralizing antibody (NAb) therapies. His team has demonstrated the safety and efficacy of mesenchymal stem cell (MSC) therapy in modulating immune responses in HIV/AIDS patients, particularly those classified as immune non-responders (INRs). MSC transfusion significantly improved immune reconstitution in these patients [7]. Moreover, HLA-mismatched allogeneic adoptive immune therapy (AAIT) was shown to increase CD4 counts and reduced opportunistic infections [8], revealing its potential in addressing severe immune dysfunction in INRs.

Moog Christian reviewed current paradigms in HIV-1 vaccine research and development, highlighting advances in both NAbs and non-neutralizing anti-V1V2 antibodies for protection. The ANRS/VR106 phase I trial investigated the CD40-HIVRI.Env vaccine, which consists of a gp140 Env fused with a humanized anti-CD40 mAb designed to target dendritic cells for better eliciting anti-V1V2 antibodies, including the IgG3 isotype. The CD40.HIVRI.Env was well tolerated, and Env-specific $CD4^+$ T-cells producing IL-2^+, IFN-γ^+, or TNF^+ were detected in all vaccinees from week 6 to week 26, and persisted until week 48 without evidence of a dose–response relationship or enhancement by DNA-HIV-PT123 co-administration. Tier-1 A MW965.26 NAb titres were detectable in 50–100% of vaccinated individuals at week 26, with one participant developing NAbs against five Tier-2 viruses. His findings suggest that CD40-targeting Env-based vaccines could play a role in inducing some potentially protective immune responses with prime-boost strategies [9].

Shan Lu provided a comprehensive review of several Phase II/III HIV vaccine clinical trials and explored potential correlates of immune protection. He emphasized the critical role of functionally selected multivalent gp120 vaccines in heterologous prime-boost vaccination strategies. He reported the safety and immunogenicity of a polyvalent DNA–protein HIV vaccine featuring matched Env immunogens, which was evaluated as both a prime–boost regimen and a co-administered approach in HIV-uninfected

Table 1. Summary of the Research Reports in Grand Challenges on HIV/AIDS in China.

Section	Research topic	Principle investigator	References
Keynote speech	Clinical progress in ART-free HIV-1 virological control and immune therapy	Fusheng Wang	[7, 8]
	Paradigms in HIV-1 vaccine research and development	Moog Christian	[9]
	Comprehensive review of HIV vaccine clinical trials and potential correlations of immune protection	Shan Lu	[10, 11]
AIDS clinical prevention and treatment	Progress in the prevention and treatment of antivirals and drug combinations in HIV-1 infected patients in China	Xiaoping Tang, Yaokai Chen, Jun Chen, Xiaojie Huang, Hong Shang, Fujie Zhang	[12, 16–18, 23]
	Progress on gp120- and gp41-targeting antiviral fusion peptides and HIV-1 fusion-inhibitory lipopeptide LP-98	Yuxian He, Jing Xue	[13]
	Prevalence of subtypes, drug-resistant variants, rates of PDR, and transmission rate of DRMs among HIV-1-infected individuals	Linghua Li, Hui Xing	[14, 15]
	Incomplete immune reconstitution in HIV/AIDS patients in China	Taisheng Li	[19–21]
	Nicotinamide mononucleotide impacts HIV-1 infection by modulating immune activation	Zhiwei Chen, Yufei Mo	[22]
HIV/AIDS pathogenesis and latency	Overview on the establishment and maintenance of HIV-1 latent reservoir	Kai Deng	[24–29]
	Regulatory factors related to HIV-1 production and latency	Guoxin Liang, Wenyan Zhang, Dan Yu, Xianghui Yu, Jianhua Wang	[30–34, 40–45]
	The role and mechanism of aging in HIV infection	Yongtang Zheng, Hongyi Zheng,	[35, 36]
	Characteristic of regulatory factors and specific T cells related to HIV-1 infected patients	Chao Zhang, Fusheng Wang	[37–39]
ART-free HIV-1 virological control	Techniques for measuring HIV-1 reservoir and clinical studies on HIV-1 functional cure	Hui Zhang, Jianqing Xu, Hongzhou Lu	[46–53]
	Purging viral latency by arsenic trioxide and HSV-vectored therapeutic vaccine in SIV-infected Macaques	Ling Chen, Caijun Sun	[54–55]
	Mechanisms of special regulatory factors and T cells in controlling the HIV-1 reservoirs	Qiankun Wang, Huanzhang Zhu, Liang Cheng, Ting Pan, Dan Mu, Linqi Zhang, Fusheng Wang	[56–63]
HIV-1 vaccine research and development	Preclinical and NMPA-approved Phase I and Phase II clinical trial studies of HIV-1 vaccines in China	Zhiwei Chen, Hui Wang, Xia Jin, Hongzhou Lu, Yiming Shao, Tong Zhang, Hao Wu, Bei Yang	[64–67, 79, 80]
	The design of vaccine immunogen focused on HIV-1 envelope protein and Bacterium-like Particles	Linqi Zhang, Feng Gao, Xianghui Yu, Ling Chen, Qinxue Hu	[71–77]
	Engineering of an AAV-vectored tandem bispecific neutralizing antibody and Anti-CD4 Nanobody against HIV-1 infection	Zhiwei Chen, Xilin Wu, Zhiwei Wu	[68–70]
	Characterization of A humanized mouse vaccination model to memory B cell reaction and A Prime-Boost vaccination approach to memory CD8+ T cell reaction	Sai Luo, Zhiwei Chen	[78]

adults in the United States (HVTN 124) [10]. In addition to inducing anti-V2 antibodies, the vaccine regimen successfully elicited a CD4-binding site (CD4bs) monoclonal antibody, HmAb64, from a human volunteer. HmAb64 was capable of neutralizing 10% of 208 HIV-1 pseudovirus strains, including tier-2 strains from clades B, BC, C, and G [11].

AIDS clinical prevention and treatment

Xiaoping Tang discussed recent progress in the prevention and treatment of fungal infections among PLWHA in China, with a particular focus on the national guidelines on AIDS diagnosis and treatment published in 2024. Highlighting the challenges posed by drug toxicity and resistant fungal infections, Tang's team emphasized the importance of early diagnosis and optimization of treatment regimen tailored to individual fungal species. Notably, pathogenic filamentous fungi were identified in 16.6% (119/716) of HIV-1-infected individuals. However, invasive fungal diseases were rare among those on ART who had achieved immune reconstitution, with $CD4^+$ T cell count (CD4 count) exceeding 200 cells/μl [12]. The recent introduction of long-acting antivirals has significantly enhanced HIV-1 prevention strategies. Yaokai Chen and Jun Chen shared insights on leveraging these new drugs, including Cabenuva, Lenacapavir and Islatravir, to simplify ART regimens, improve adherence, and boost treatment efficacy among Chinese patients. Regarding domestically developed injectable treatments, Yuxian He reported progress on gp120- and gp41-targeting antiviral fusion peptides and bifunctional molecules anchored to the surface of target cells via glycosylphosphatidylinositol, offering counter measures against HIV-1 escape and resistance for cure research. Yuxian's team also developed the HIV-1 fusion-inhibitory lipopeptide LP-98, which exhibits potent and long-acting antiviral activity. LP-98 monotherapy significantly reduced viral loads and sustained long-term viral suppression in $SHIV_{SF162P3}$-infected macaques [13]. Furthermore, when administered as pre-exposure prophylaxis (PrEP) at 2-hour and 1-week but not at 2-week prior to viral challenge, LP-98 provided complete protection against $SHIV_{SF162P3}$ and SIV_{mac239} infections in 51 rhesus monkeys challenged via intrarectal, intravaginal, or intravenous routes [13]. Jing Xue added that several biological pathways may underlie LP-98's early treatment protection. These pathways include genes related to lipoprotein particle response, cellular response to lipoprotein particle stimulus and detection of biotic stimulus.

Linghua Li presented findings on the prevalence of HIV-1 subtypes and drug-resistant variants among 6831 HIV-infected treatment-naïve individuals in Guangdong province between 2018 and 2022. The drug-resistant mutations (DRMs) were identified in 24.5% of the patients, while the prevalence of pretreatment drug resistance (PDR) was 7.4%. The resistance rates to nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) were 1.3%, 4.8%, and 1.4%, respectively. These findings suggested that PDR and measurable viremia during ART underlie treatment failure and a high incidence of drug resistance, reaching up to 50% [14]. Hui Xing from the China CDC reported that the prevalence rates of PDR to NNRTI, NRTI and PI were 6.3% ($n = 163$), 1.2% ($n = 32$), and 0.2% ($n = 5$), respectively. Furthermore, the transmission rate of DRMs, particularly to NNRTIs, has risen from 2.6% (2004–2006) to 7.8% (2021–2022), based on nation-wide sequence data from nearly 60,000 untreated patients. In some provinces, this rate has exceeded 20%, correlating with increased rates of ART-failure (adjusted odds ratio [AOR] = 2) and mortality (AOR = 4.25). These trends post significant challenges for AIDS prevention efforts in China [15]. Xiaojie Huang introduced the national guideline for PrEP, which was recommended in 2021. However, even among high-risk populations, less than 20% of total MSM were aware of PrEP, and less than 1% used PrEP and post-exposure prophylaxis (PEP), highlighting a significant awareness gap in HIV-1 prevention. Moreover, a study involving 1933 participants revealed that MSM in China prefer both daily and on-demand PrEP when provided for free of charge [16]. In the China Real-world Study of Oral PrEP (CROPrEP), Hong Shang reported that long-acting injectable PrEP (LAI-PrEP) shows promise for expanding PrEP coverage. However, former CROPrEP participants with suboptimal adherence to oral PrEP were less likely to opt for LAI-PrEP [17]. Additionally, young and well-educated Chinese MSM, despite being high-risk for HIV-1 infection, reported a low willingness to uptake PrEP [18]. These findings underscore the need for enhanced implementation efforts to increase PrEP and LAI-PrEP uptake among MSM in China.

Taisheng Li previously reported that only 40.5%, 44.2% and 50.6% patients achieved CD4 count greater than 500 cells/μl after 3-years, 5-years and 10-years of ART, respectively, in a cohort of 662 subjects [19]. Incomplete immune reconstitution has been identified as a significant risk factor contributing to the annual 30,000–40,000 HIV-1-associated deaths in recent years in China. Incomplete immune reconstitution is known to have an increased risk of clinical progression and mortality [20]. Addressing this issue, the 2024 edition of Chinese Guidelines for the Diagnosis and Treatment of HIV/ AIDS has included recommendation on management of incomplete immune reconstitution [21]. Notably, Yufei Mo and Zhiwei Chen recently demonstrated that combined ART and nicotinamide mononucleotide (NMN) treatment suppressed hyperactivation of T cells and significantly increased CD4 count in an HIV-1/humanized mouse model, paving the way for future clinical trials [22]. Fujie Zhang reported that the implementation of the "Four Free and One Care" policy since 2003 has led to significant declines in mortality and improvements in prognosis for PLWHA, including infected children and adolescents in China (https://doi.org/10.1016/j.heliyon.2024.e27961). Recently, a switch from previous NNRTI-based regimen to ANV/3TC/TDF resulted in less weight gain and improved lipid metabolism while maintaining virological suppression comparable to that of EVG/Cobi/FTC/TAF in a phase 3 trial [23].

HIV/AIDS pathogenesis and latency

Kai Deng provided an overview on the establishment and maintenance of HIV-1 latent reservoir, with a focus on targeted strategies of eliminating latency cells [24]. His team developed a novel dual fluorescent reporter virus, called DFV-B, which enables direct labelling of latently infected cells in primary $CD4^+$ T cells and the generation of a physiological relevant latency model. Using this model, they identified ACY-1215 (also called Ricolinostat) as a potent latency reversing agent, a finding that was further validated in primary $CD4^+$ T cells from ART-suppressed individuals *ex vivo* [25]. Notably, Ricolinostat is the first oral selective histone deacetylase 6 (HDAC6) in clinical trials against multiple myeloma [26]. Additionally, the team discovered that methionine adenosyl transferase 2A (MAT2A)-mediated one-carbon metabolism plays a regulatory role in HIV-1 latency [27]. They demonstrated that the quantification of singly spliced HIV-1 vpu/env mRNA is practical approach for measuring intact viruses [28]. Furthermore, they reported an FDA-approved drug, ponatinib, that can broadly repress latent HIV-1 reactivation in various cell models by inhibiting the activation of the AKT-mTOR pathway [29]. Guoxin Liang previously reported that the cell membrane metalloprotease TRAB domain-containing protein 2A (TRABD2A) inhibits HIV-1 production in resting $CD4^+$ T cells by degrading the virion structural precursor polyprotein Gag at the plasma membrane. Depletion or inhibition of TRABD2A's metalloprotease activity significantly enhanced HIV-1 production in resting $CD4^+$ T cells. Their findings elucidate the molecular mechanism by which resting $CD4^+$ T cells potently restrict the assembly and production of HIV-1 progeny [30]. Subsequently, Liang's team discovered that TRABD2A also restricts HIV-1 production in monocyte-derived

dendritic cells [31]. More recently, they identified that interleukin-4 (IL-4) may promote HIV-1 infection in macrophages by downregulating Connexin26 (CX26), a protein that regulates viral attachment to target cells. Wenyan Zhang discovered that the ribosomal protein lateral stalk subunit P1 (RPLP1) in long-term non-progressors (LTNPs) might inhibit HIV-1 transcription by occupying the C/EBPβ binding sites in the long terminal repeat (LTR). The HIV-1-induced translocation of RPLP1 from the cytoplasm to the nucleus is critical for its antiviral activity. Consequently, knockdown of RPLP1 could promote the reactivation of latent HIV-1. Notably, HIV-1 group M subtype C and group N, O and P strains, which do not require C/EBPβ for transcription, are exceptions [32]. Wenyan's team also reported that deubiquitinase USP37 enhances the anti-HIV-2/SIV ability of the host restriction factor SAMHD1 [33], while USP3 inhibits HIV-1 replication via promoting APOBEC3G expression through both enzyme activity-dependent and -independent manners [34]. Dan Yu presented findings on the interaction between the protein arginine methyltransferases 3 (PRMT3) and the HIV-1 LTR. Depletion or inhibition of PRMT3 was shown to suppress Tat-induced transactivation of HIV-1 transcription via the PRMT3/TEAD4/P-TEFb axis.

Yongtang Zheng and Hongyi Zheng investigated SIV_{mac239} infection in six young and six old Chinese rhesus macaques (ChRMs). Old ChRMs exhibited more severe SIV production and CD4/CD8 ratio inversion than younger ChRMs in both peripheral blood and lymph nodes. This was particularly evident when a large number of $CD8^+$ T cells infiltrated the follicles and germinal centres. Aging appears to be a cofactor contributing to SIV-induced immune disorders in secondary lymphoid tissues, impairing the effective antiviral activity of highly enriched follicular $CXCR5^+CD8^+$ cells [35]. The researchers also studied ART outcomes in aged PLWHA. Consistently, older participants exhibited significantly lower $CD4^+$ T-cell counts and reduced $CD4^+/CD8^+$ recovery post-ART, with only 32.21% achieving immune reconstitution compared with younger (52.16%) and middle-aged patients (39.29%) at the end of follow-up period [36]. These findings highlight the need for tailored interventions and comprehensive management strategies for older patients with HIV.

Chao Zhang presented that NLRP3 inflammasome activation, driven by virus-dependent and/or -independent ROS production, promotes $CD4^+$ T cell pyroptosis in chronically infected individuals. This was demonstrated by simultaneously monitoring caspase-1 and caspase-3 activation in circulating $CD4^+$ T cells [37]. NLRP3-dependent pyroptosis may contribute to $CD4^+$ T cell loss in HIV-1-infected patients, highlighting pyroptosis signalling as a potential target for anti-HIV-1 treatment. Additionally, Fusheng Wang's team also revealed that intrafollicular accumulation of $CXCR5^+$ natural killer (NK) cells may exhibit anti-HIV-1 effects through the upregulated expression of CD107a and β-chemokines [38]. Furthermore, global transcriptomic profiling of T cells uncovered dysregulated pathways associated with chronic immune activation and exhaustion [39]. $CD4^+$ and $CD8^+$ Effector-GNLY clusters were expanded in untreated individuals and remained persistently increased in ART-treated individuals, correlation with poor immune restoration. Xianghui Yu demonstrated that HIV-1 Nef exhibited varying abilities to antagonize the serine incorporator 5 (SERINC5) [40]. Her team also reported that SERINC5 inhibits HIV-1 transcription by negatively regulating NF-κB signalling, mediated by the retinoic acid-inducible gene I-like receptors, MDA5 and RIG-I. By recruiting TRIM40 as an E3 ubiquitination ligase, SERINC5 promotes K48-linked polyubiquitination and proteasomal degradation of MDA5 and RIG-I. This process impedes the nuclear translocation of the p50/p65 dimer, thereby repressing HIV-1 LTR-driven gene expression [41]. Recently, her team engineered functional CD8 T cells using the synNotch receptor CD4-17b to recognize HIV-1 Env. These engineered T cells activate the expression of broadly neutralizing antibody (bnAb) VRC01 and the bispecific T-cell engager (BiTE) N6-aCD3, resulting in enhanced anti-HIV activities. Jianhua Wang demonstrated that long noncoding RNA MALAT1 releases epigenetic silencing of HIV-1 replication by displacing the polycomb repressive complex 2 from binding to the LTR promoter [42]. Furthermore, their research revealed that the activation of Aryl Hydrocarbon Receptor-mediated signalling can reactivate HIV latency [43]. Additionally, they identified that the X-linked RNA-binding motif protein modulates HIV-1 infection in $CD4^+$ T cells by maintaining the tri-methylation of histone H3 lysine 9 (H3K9me3) at the downstream region of the 5′ LTR of HIV proviral DNA [44]. Recently, the team found that the Wnt downstream β-catenin/TCF1 pathway serves as a crucial modulator for HIV-1 latency. Pharmacological activation of the β-catenin/TCF1 pathway using glycogen synthase kinase-3 (GSK3) inhibitors promoted the transcription of HIV-1 proviral DNA and successfully reactivated latency in $CD4^+$ T cells [45]

ART-free HIV-1 virological control (or functional cure)

Hui Zhang, the scientist who introduced the concept of "HIV-1 deep reservoir," provided a comprehensive review on current techniques for measuring the inducible reservoir and deep reservoir. These techniques include proviral DNA analysis, cell-associated viral RNA detection, the intact proviral DNA assay (IPDA), integration site detection, virus outgrowth

assay (VOA), epigenetic markers, among others. In a study of 14 participants who received bnAb-derived CAR T cells, his group found that the therapy was safe and well tolerated. However, viremia rebound occurred in all six participants who discontinued ART, with a medium rebound time of 5.3-week. Despite that, cell-associated viral RNA and intact proviruses decreased significantly following the CAR T cell treatment. All viral rebounds were attributed to preexisting or emergence of viral escape mutations [46]. Through the testing of 126 upregulated plasma membrane proteins in HIV-1 latently infected cells, his team identified CD98 as a potential biomarker for HIV-1 latently infected cells, which could help evaluate the effect of various strategies aimed at reducing the viral reservoir [47]. Using the CRISPR affinity purification *in situ* of regulatory elements (CAPTURE) system, they identified that origin recognition complex 1 (ORC1), the largest subunit of the origin recognition complex, contributes to HIV-1 latency in addition to its role in DNA replication initiation [48]. Furthermore, they discovered that CBX4, a component of the Polycomb Repressive Complex 1 (PRC1), facilitates HIV-1 latency in seven latency models and primary $CD4^+$ T cells by forming nuclear bodies on the LTR [49].

Jianqing Xu has developed a novel anti-HIV-1 CAR-T cell therapy, termed M10 cells, which are armed with a potent CAR, bnAbs and the follicle-homing receptor CXCR5. These cells exhibit three biological functions: broad and potent cytotoxicity against HIV-infected cells, neutralization of cell-free viruses, and homing to B-cell follicles. M10 cells were administered to 18 HIV-1 patients as part of a treatment regimen involving two allogenic infusions spaced 30 days apart, followed by two chidamide stimulations to reactivate the HIV-1 reservoir. No significant treatment-related adverse effects were observed. In 74.3% of cases, M10 cell infusions led to substantial suppression of viral rebound, with viral loads decreasing by an average of 67.1%. Additionally, 10 patients showed a sustained reduction in cell-associated HIV-1 RNA levels over a 150-day observation period, with an average decrease of 1.15 log10. M10 cells also exert selective pressure on the latent viral reservoir [50].

Hongzhou Lu presented several clinical studies. In a single-centre study, 15 cancer patients were treated with chemotherapy and/or other oncological therapies in conjunction with cART, prior to receiving immune checkpoint inhibitor (ICI) such as Sintilimab, Nivolumab, or Camrelizumab [51]. The results showed that ICIs had favourable response with manageable side effects, and did not lead to deteriorated effects on plasma HIV-RNA and CD4 count. In a single-arm prospective study of 20 immune non-responders, thymosin α1 was found to enhance $CD4^+$ T cell count and thymic output, though this effect was only observed as a trend [52]. The combination of the anti-PD-L1 antibody ASC22 and the histone deacetylase inhibitor chidamide was tested as a "shock and kill" strategy. This treatment combination was well-tolerated and appeared effective in activating latent HIV reservoirs. However, it did not succeed in enhancing the function of HIV Gag/Pol-specific $CD8^+$ T cells. A negative correlation was observed between the proportions of HIV Gag-specific effector memory T cells (TEM) and changes in integrated DNA in subjects who exhibited improvement in T cell function [53].

Ling Chen reported that arsenic trioxide (As2O3), when combined with ART, effectively reactivated the viral reservoir and delayed viral rebound after ART interruption in chronically SIV-infected macaques. Additionally, As2O3 treatment restored CD4 count, delayed disease progression, and improved survival in acutely SIV-infected macaques. As2O3 monotherapy significantly increased the CD4/CD8 ratio, enhanced SIV-specific T cell responses, and reactivated viral latency in chronically SIV_{mac239}-infected macaques. Notably, As2O3 specifically induced apoptosis in SIV-infected $CD4^+$ T cells. These findings provide valuable insights into the potential use of As2O3 as a component of the "shock and kill" strategy [54]. Caijun Sun reported their findings on herpes simplex virus type I (HSV-1). His team revealed ICP34.5 of HSV-1 acts as an antagonistic factor for HIV-1 reactivation by promoting the phosphorylation of HSF1, which in turn binds to the HIV-1 LTR. HSV-ΔICP34.5, therefore, may activate HIV-1 latency through the NF-κB pathway. Furthermore, recombinant HSV-ΔICP34.5 expressing the fusion sPD1-SIVgag protein successfully activated viral latency and simultaneously stimulated antigen-specific T-cell immune responses, delaying viral rebound after ART interruption in chronically SIV-infected macaques [55].

Qiankun Wang discovered that human CARD8, a member of the caspase recruitment domain (CARD)–containing family of innate immune sensors, can be activated through the proteolysis of its N-terminus by HIV-1 protease [56]. Thus, CARD8 functions as an inflammasome sensor for HIV-1 protease activity. When infected cells were treated with a potent NNRTI, intracellular Gag-Pol dimerization was enhanced, leading to CARD8-mediated caspase activation and pyroptosis. Sensing of HIV-1 protease activity by CARD8, trigger rapid pyroptosis in infected quiescent cells, influencing HIV/SIV pathogenesis and disease progression [57]. Targeting the CARD8 inflammasome could provide a novel strategy for eliminating residual HIV-1-infected cells, prompting further investigation of NNRTI-induced CARD8

activation *in vivo*. Huanzhang Zhu presented advancements in zinc-finger nucleases (ZFNs) controlled by the HIV-1 LTR. Functional expression of ZFNs, induced by Tat, successfully excised integrated proviral HIV-1 DNA in approximately 30% of infected cells [58]. More recently, the team developed a viral-like particle (VLP) mRNA delivery system, designated as ENV-ZFN-VLP, which excised HIV-1 provirus *in vivo* without causing off-target effects. The team also engineered HIV-specific CAR-T cells, including the 3BNC117-E27 CAR construct, which incorporate a PD-1-blocking scFv E27 and the single-chain variable fragment of the 3BNC117 to specifically target native HIV-1 Env. These 3BE CAR-T cells demonstrated cytotoxic activity against Env^+ cells in NSG mice [59]. Furthermore, Liang Cheng developed a fusion protein, hyperIL-15×sCD4-Fc, by combining hyperIL-15 and sCD4 with human IgG1-Fc as a heterodimer. This fusion protein effectively reactivates the HIV-1 reservoir in latently infected cells and in HIV-1-infected humanized mice on ART. Additionally, it may enhance cytotoxic T lymphocyte (CTL) and antibody-dependent cellular cytotoxicity (ADCC) responses, potentially aiding in the eradication of latent reservoir cells.

Ting Pan presented findings on the histone chaperone chromatin assembly factor 1 (CAF-1), which is enriched on the HIV-1 LTR and forms nuclear bodies with liquid–liquid phase separation properties. CAF-1 nuclear bodies recruit epigenetic modifiers and histone chaperones, thereby establishing and maintaining HIV-1 latency in various latency models and primary $CD4^+$ T cells. The formation of CAF-1 nuclear body is critical for maintaining HIV-1 latency, and disrupting these phase-separated structures could serve as a potential strategy to reactivate latent HIV-1 [60]. Dan Mu reported a previously uncharacterized role of TRIM5α in maintaining viral latency. Knockdown of TRIM5α enhanced HIV-1 transcription in multiple latency models, an effect that was reversed by shRNA-resistant TRIM5α. Mechanistically, TRIM5α binds to the HIV-1 LTR and promotes the recruitment of histone deacetylase 1 (HDAC1) to NF-κB p50 and Sp1, contributing to the suppression of viral transcription [61].

Linqi Zhang focused on developing a diverse repertoire of TLR7/8 agonists to identify more potent candidates for activating latent HIV-1 reservoirs as well as enhancing NK and T cells activity. Among the compounds screened, two TLR7/8 dual agonists and one TLR8-specific agonist demonstrated exceptionally high potency in reactivating latent HIV-1 in cell lines and PBMCs from patients with persistent and durable virologic control [62]. Fusheng Wang's team identified an unconventional population of $CD45RA^+$, $PanKIR^+$, and/or $NKG2A^+$ virtual memory $CD8^+$ T cells (T_{VM} cells) that play a role in controlling the HIV-1 reservoir during antiretroviral therapy (ART). These Tvm cells can suppress the viral reservoir by preventing HIV-1 reactivation through KIR-mediated recognition [63], highlighting their potential role in reservoir control.

HIV-1 vaccine research and development

Zhiwei Chen reviewed the major milestones in HIV/AIDS research over the past 43 years, emphasizing that the lack of HIV vaccine and therapeutic cure remain to be grand challenges in the field. He presented preclinical studies of a PD1-enhanced DNA vaccine, designed to target dendritic cells for improved antigen cross-presentation and the induction of effector memory CD8 T cells [64]. This approach achieved an over 6-year period of ART-free virologic control in monkeys [65,66]. Hui Wang, Hongzhou Lu, Xia Jin and Zhiwei Chen collaborated on a NMPA-approved Phase I clinical trial results of 45 PLWHA on cART using the PD1-enhanced DNA vaccine ICVAX, which encodes conserved bivalent mosaic Gag antigens [67]. The trial demonstrated excellent safety and an immunogenicity rate of around 80% in the middle-dose cART-stable PLWHA as a therapeutic vaccine. He indicated that a phase II trial has been planned. Additionally, he introduced the engineering of an AAV-vectored tandem bispecific neutralizing antibody, BiIA-SG, which achieved sustained control of live HIV-1 in animal models [68,69]. The combination of ICVAX and AAV-vectored BiIA-SG is being explored as a potential strategy for HIV-1 prevention and curative immunotherapy. Xilin Wu and Zhiwei Wu presented their findings on a novel anti-CD4 nanobody, Nb457, cloned from a CD4-immunized alpaca. Nb457 exhibited potent and broad activity against HIV-1, surpassing the efficacy of Ibalizumab. An engineered trimeric Nb457 demonstrated complete inhibition of live HIV-1, outperforming both Ibalizumab and the parental Nb457 nanobody. Structural analysis revealed that Nb457 induces conformational changes in CD4, effectively blocking viral entry. Additionally, Nb457 showed therapeutic efficacy in humanized mouse models [70], highlighting its potential as a promising candidate for HIV-1 treatment.

Sai Luo presented a humanized mouse vaccination model featuring V(D)J-rearranging and TdTexpr R repertoires through rearrangement of VH1-2, along with Vκ1-33 and/or Vκ3-20, in combination with diverse CDR3s and human-like TdT activity in precursor B cells. Immunization with eOD-GT8 60mer in this model effectively engaged VRC01 precursors, inducing robust VRC01-class germinal centre B cell responses. This innovative class of mouse models represents a valuable tool for the preclinical evaluation of candidate HIV-1 vaccination strategies. Qinxue Hu

developed a series of fusion CLD proteins that exhibit broad neutralizing activity against HIV-1 infection, with potency comparable to or exceeding that of the highly effective HIV-1 bnAbs reported to date [71]. Additionally, the team engineered a Tat-dependent conditionally replicating adenovirus that selectively replicates and expresses the diphtheria toxin A chain (Tat-CRAds-DTA). This virus demonstrated the ability to specifically target and kill HIV-1-infected cells both in vitro and in humanized mice. These innovative constructs hold promise for further development as potential prophylactic or therapeutic strategies against HIV-1 infection [72].

Linqi Zhang characterized uncleaved prefusion-optimized (UFO) trimers for 12 HIV-1 Envs currently circulating in China. Among these, two subtype B Envs, CNE6 and MG13, demonstrated the highest trimer content and stability, comparable to the well-studied subtype A reference, BG505, as confirmed by negative-stain electron microscopy (*59*). Notably, a single gp41 substitution, E658 K, was identified as the major determinant in shaping the neutralization profile and the overall conformation of Env during viral adaptation [73]. Additionally, the team reported a panel of HIV-1 strains exhibiting broad and potent resistance to a wide range of bnAbs, particularly those targeting the CD4-binding site (CD4bs). Several key epitope mutations contributing to this resistance were identified in the inner domain, loop D, and β23/loop V5/β24 regions of gp120 [74]. These insights are valuable for the design of vaccine immunogen aimed at overcoming antibody resistance and improving efficacy. Feng Gao developed a novel HIV-1 envelope glycoprotein nanoparticle (Env/NP) vaccine using amphiphilic polymers. This vaccine elicited more potent and broader neutralizing activities against multiple HIV-1 subtypes [75]. Additionally, the team also designed consensus Env sequences to express stable trimers representing five critical time points prior to the emergence of bnAbs. Their immunization strategy involved priming with the transmitted/founder Env timer, followed by sequential boosting with these consensus Env trimers. This approach induced broader and more potent bnAbs targeting the gp120/gp41 interface in guinea pigs [76], highlighting its potential for future HIV-1 vaccine development.

Xianghui Yu and Ling Chen demonstrated that a vaccine composed of bacterium-like particles (BLPs) displaying Protan-gp120AE-MTQ (PAM) induced HIV-1-specific sIgA following intranasal immunization. Subsequent intramuscular boosting elicited serum neutralizing antibodies against heterologous HIV-1 tier 1 and 2 pseudoviruses [77]. In the context of vaccine-induced tissue-resident memory T (TRM) cells for mucosal protection, Zhiwei Chen previously reported that central memory T cells induced by intramuscular DNA vaccine priming, served as major precursors for lung Gag-specific TRM cells [78]. These cells were established following a boost with an intranasal live-attenuated influenza-vectored vaccine. This work provides valuable insights for optimizing mucosal vaccine strategies to enhance protective immunity [78]. Yiming Shao, Tong Zhang, Hao Wu, and colleagues conducted a phase II clinical trial involving DNA priming at 0, 4, and 8 weeks, followed by a recombinant Tiantan vaccinia (rTV) vaccine boost at week 16 in 150 volunteers at Beijing Youan Hospital. The vaccines, which express HIV-1 CRF 07 gag, pol, and env genes, were well tolerated with no serious adverse events (SAE) reported. They induced strong HIV-1 specific antibody responses in 100% of participants and robust T-cell responses in 60%. While the vaccines elicited a strong antibody response to the V1V2 loop, they generated minimal neutralizing antibody responses [79]. Additionally, Yiming Shao and Bei Yang reported cryo-EM structures of Envs from two circulating recombinant forms, CRF01_AE and CRF07_BC, at 3.0 and 3.5 Å, respectively. They identified unique features of CRF01_AE V1 region, associated with the resistance to certain bnAbs. Furthermore, the 4.1 Å cryo-EM structure of CRF01_AE Env in complex with F6 revealed a gp120-gp41 spanning epitope that allosterically destabilizes the Env trimer apex, weakens inter-protomer packing, and hinders the receptor binding, leading to Env trimer disassembly. These findings provide critical insights into the structural biology of CRF Envs and inform future HIV-1 vaccine design [80].

Future perspectives

Mengjie Han presented the epidemiology of HIV/AIDS in China at the 4th GCHAC Symposium. By the end of 2022, the diagnosed number of PLWHA was 1.223 million, a figure that has remained relatively unchanged since 2018, when it was estimated as 1.23 million [81]. Similarly, the number of HIV-1-associated deaths in 2018, estimated at approximately 35,000 (95% UI: 30,000–41,000), remains comparable to recent reports. Critically, among young PLWHA aged 15-24, 77.8% were out-of-school youth, who face a higher risk of infection compared to MSM attending colleges. Additionally, the proportion of newly reported cases among male individuals aged 50 and older rose significantly from 19.57% in 2010 to 44.39% in 2022 [82]. Meantime, the proportion of female cases in the 50-and-older group increased dramatically from 16.26% in 2010 to 62.78% in 2022 [82]. Alarmingly, only 56.2% of participants in one study reported attending HIV-1 counselling and testing within the past 12 months [83]. These findings, combined with less than 85% diagnostic rate [84], suggest that the number of PLWHA in China is unlikely to drop below the current 1.33 million by 2030, which requires an estimated annual cost burden of 6.3 billion

RMB for ART alone (estimated annual 5000 RMB per PLWHA). As a result, achieving the goal of ending HIV/AIDS in China by 2030 appears increasingly unlikely. Sustained financial investment in treatment-as-prevention strategies, effective preventive interventions, and research into vaccines and cures will be essential through 2050 and beyond to control the epidemic more effectively.

China is at a pivotal moment as it formulates the 15th Five-Year Plan, which will significantly influence the trajectory of HIV/AIDS control efforts. The recent global failure of multiple phase III trials for preventive HIV-1 vaccines highlights the urgent need for a major scientific breakthrough in eliciting bnAbs and broadly protective T cell immunity. Preventive vaccine candidates that fail to elicit bnAbs in phase I-II trials are unlikely to succeed in future phase III trials, given that sterile protection has been consistently demonstrated only through prior passive immunization with potent bnAbs. In addition to focusing on vaccine antigen design, such as the development of physiologically relevant spike trimers, it is equally critical to explore why the majority of B cell receptors fail to respond to bnAb-reactive trimers. Drawing lessons from COVID-19 vaccine development, it may also be worth considering whether the goal of prophylactic HIV-1 vaccine could shift from preventing HIV-1 infection to preventing AIDS. This approach, supported by non-human primate studies, has shown promise for achieving sustained ART-free virological control even after breakthrough infections. Balancing these scientific insights with practical strategies will be essential to advance vaccine research and improve the prospects of HIV/AIDS control in the coming years. With more and more basic discoveries advanced into human studies, it is urgently needed to establish a national clinical trial network and associated good laboratory practice (GLP)-certified laboratories where validated assays can be performed to support translational research.

In China, no cases of HIV-1 cure have been achieved due to the absence of natural bone marrow donors with homozygous CCR5 deletion. To address this, CRISPR-edited CCR5-ablated haematopoietic stem and progenitor cells (HSPCs) were tested in a Chinese patient with HIV-1 infection and acute lymphoblastic leukaemia [85]. Although the percentage of CCR5 disruption in lymphocytes was only approximately 5%, this study provides a promising foundation for future HSPC-based cure research. Until now, the precise source of HIV-1 rebound after stopping ART remains largely unknown. Like elite controllers, vaccine-induced sustained ART-free virological control will require potent and protective T cells distributed across multiple tissue compartments, including mucosal lymph tissue and bone marrow. However, finding from animal studies such as those utilizing AD26- and CMV-based vaccines have yet to be successfully reproduced in humans. More investigator-initiated trials are urgently needed to yield biologically relevant insights for cure research. In addition to strategies such as "shock and kill" and "block and lock," gene therapy approaches, including latency-targeted gene editing and reservoir depletion should be actively explored. These innovative strategies hold the potential to pave the way for new therapeutic avenues and, ultimately, a cure for HIV-1.

In summary, we have highlighted the ongoing efforts of GCC scientists in combating HIV/AIDS in recent years. While the goal of ending HIV/AIDS by 2030 remains challenging, greater emphasis will be placed on treatment-as-prevention strategies, novel effective preventive interventions, and in-depth research on vaccines and cures. Notably, increasing the coverage of high-risk individuals to use long-acting injectable PrEP will be a key focus especially in resource-limiting areas. While two more PLWHs were recently cured following the CCR5-delta 32 stem cell transplantation, the case of the "Geneva patient" who achieved a cure after receiving stem cells with wild-type CCR5 further encourages cure research beyond CCR5 disruption and strategies for sustained virological control.

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