

# Multidisciplinary collaborative integrated management of increasingly prominent HIV complications in the post-cART era

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## Objectives

With the prolonged survival time of AIDS patients, complications of various systems and organs of HIV infection are increasingly prominent. These diseases have become the major factors influencing the quality of life and prognosis of HIV-infected persons, and multidisciplinary cooperation treatment is urgently needed.

## Methods

The Chinese HIV/AIDS Clinical Trial Network has conducted a series of multicentre clinical cohort studies over the past 16 years, in which studies related to people living with HIV systemic complications. Based on the results of previous studies, this review establishes the complications of Chinese people living with HIV after long-term cART.

## Results

HIV's direct damage to human cells, chronic abnormal inflammatory activation after HIV infection, long-term drug side effects caused by cART and persistent reservoirs cause systemic complications in people living with HIV. We summarised the clinical characteristics of the complications of HIV infection in China from the aspects of the liver, cardiovascular, the nervous system, the kidney, bone metabolism, blood glucose, and lipid metabolism.

## Conclusions

The management of the complications of HIV infection is a major link in improving the survival treatment and prognosis of patients in the future. The joint participation of doctors from different departments of general hospitals in the management of comorbidities is the main theme for future improvement of quality of life and prognosis for people living with HIV.

**Keywords:** AIDS, cardiovascular, cognitive disorder, complication, HIV, osteoporosis

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## Introduction

Combination antiretroviral therapy (cART) can effectively control virus replication in people living with HIV (PLWH), which, in turn, develops into AIDS, a chronic

infectious disease. The length of survival is not the primary concern of HIV-infected patients who are currently receiving treatment. The advent of cART and the introduction of early antiviral therapy have greatly reduced both the incidence of opportunistic infections and tumours in PLWH. While the survival period of patients with AIDS continues to improve, the persistence of the virus reservoir, abnormal immune activation and lifelong administration of HIV medication make patients more prone to heart, nerve, kidney, metabolism and other system and organ complications, defined as various non-AIDS-defining diseases (NADs). The comorbidities of both HIV- and non-HIV-infected patients have different

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clinical characteristics. The difference of the cART regimen has different effects on organs and complications among patients. During the post-cART era, these diseases have become the principal factors that affect the quality of life and prognosis of PLWH; therefore, it is urgent to conduct comprehensive treatment through multidisciplinary cooperation. The Chinese guidelines for diagnosis and treatment of HIV/AIDS (2018) proposed a whole-process management of HIV infection for the first time, which refers to a whole-process comprehensive diagnosis and treatment and service care management mode provided by a multidisciplinary team after HIV infection is diagnosed [1].

The Chinese HIV/AIDS Clinical Trial Network (CACT) was established in 2004, initially involving 17 medical and health institutions. The CACT has conducted a series of multicentre clinical cohort studies over the past 16 years with the support of the Ministry of Science and Technology's National Key Technologies R&D Programme, in which studies related to PLWH systemic complications are listed (Table 1). Based on the results of previous CACT studies, this review establishes the complications of Chinese PLWH after long-term cART, aiming to provide clinicians from different departments with the clinical characteristics of the various complications of HIV infection. Moreover, we have formed a multidisciplinary team constituted by experts in infectious diseases to jointly promote the management of PLWH, namely the screening and treatment of NADs, thus improving quality and experience of life.

### Liver: coinfection and medication

In 2006, stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP) and zidovudine (ZDV) + 3TC + NVP, the initially recommended first-line regimens, were included in the first Chinese National Guidelines for HIV/AIDS Diagnosis and Treatment in China. According to data released by the China Centers for Disease Control and Prevention (CDC) in 2009, 43.9% of patients developed treatment-related hepatotoxicity, most of which occurred in the first 3 months, resulting in both a high incidence of adverse reactions and poor adherence. NVP is the leading cause of hepatotoxicity; the international guidelines for HIV/AIDS treatment usually suggest the use of NVP at the baseline CD4 count level. The use of NVP is not recommended for women with CD4 count > 250 cells/ $\mu$ L and men with CD4 count > 400 cells/ $\mu$ L; however, this conclusion does not seem to apply to Chinese AIDS patients. The CACT data showed that NVP was not recommended for baseline CD4 > 250 cells/ $\mu$ L in Chinese patients

regardless of sex, which reduced the incidence of hepatotoxicity by 50% in clinical practice [2].

People living with HIV often show either hepatitis B (HBV) or C (HCV), coinfection with the former being more prevalent in China. The average HIV/HBV coinfection rate in China is 9.5%, with eastern China showing the highest at 14.6% [3,4]. The interaction between HIV and HBV is reciprocal. HIV accelerates the progression of HBV-related liver disease, and HBV is associated with faster HIV progression. HIV/HBV coinfection was associated with an increased risk of liver fibrosis in PLWH prior to cART, which was associated with a significantly lower fibrosis score [5]. HIV/HBV coinfection does not influence the antiviral effect of HIV. Higher HBV DNA inhibition rates were obtained if baseline HBV DNA was > 20 000 IU/mL or HBeAg-positive coinfecting subjects received cART-based tenofovir (TDF) + 3TC. However, in coinfecting patients with HBV DNA < 20 000 IU/mL or HBeAg-negative, mono-3TC-based treatment was also effective over the 48-week observation period [6].

The following points should be given attention in the course of HIV/AIDS antiviral therapy-induced hepatotoxicity: prevention over treatment, baseline liver function test, using CD4 count and coinfection to evaluate liver condition, follow-up and monitoring, regular follow-up, and increased follow-up during the 6-week high-risk period prior to cART treatment, rational selection and adjustment for cART, the emphasis placed on selecting initial treatment, and timely adjustment of cART regimen in patients with – or at risk of – hepatotoxicity.

### HIV infection is an independent risk factor for atherosclerosis

HIV infection is linked to an increased risk of cardiovascular disease (CVD). Traditional cardiovascular risk factors, such as hypertension, dyslipidaemia, diabetes, smoking, obesity and advanced age, may lead to cardiac insufficiency and is more common in PLWH. Among the untreated HIV infections in China, the most common factors are dyslipidaemia and smoking, accounting for 51.7% and 23.7%, respectively. Even without traditional factors, PLWH have a higher risk of CVD than HIV-negative individuals.

HIV may impair cardiac function by directly affecting cardiomyocytes and myofibrils [7] with diastolic dysfunction (DD) being an early indicator of underlying heart disease. In a cross-sectional study of PLWH without CVD symptoms, we observed that PLWH had a higher prevalence of DD *vs.* HIV-negative controls, most of which were mild or moderate. HIV infection was independently

**Table 1** Main findings of Chinese HIV/AIDS Clinical Trial Network in HIV-infected persons in China

System or Organ	Object	Main conclusion	Reference
Liver	cART in HIV/HBV coinfection	Chronic HBV infection and isolated hepatitis B core antibody positivity were related to faster HIV progression	Wang <i>et al.</i> [3], <i>AIDS</i> . 2012
	Nevirapine hepatotoxicity	Hepatotoxicity was a common adverse effect of nevirapine among men and women with CD4 <sup>+</sup> > 250 cells/ $\mu$ L. Chinese treatment guidelines should be considered to reflect this risk	Zhang <i>et al.</i> [2], <i>J Acquir Immune Defic Syndr</i> . 2013
	Lamivudine-resistant HBV	The emergence of 3TC-resistance mutations was closely associated with high HBV DNA loads. To avoid the emergence of 3TC-resistant HBV, the monitoring of HBV DNA loads and the use of ART including TDF are recommended for patients coinfecting with HIV and HBV	Lijun Gu <i>et al.</i> [35], <i>PLoS One</i> . 2015
	Liver fibrosis scores	cART was associated with improvement in hepatic fibrosis scores in the majority of HIV-hepatitis coinfecting and HIV-monoinfecting Chinese participants	Li <i>et al.</i> [5], <i>Medicine</i> . 2016
	Prevalence of HBV and HCV	HBV and HCV prevalence rates are high in HIV-positive Chinese and differ by geographic region. HBV and HCV coinfection and HIV monoinfection are risks for moderate-to-significant liver disease. Only HIV/HBV is associated with greater HIV-related immunosuppression	Xie <i>et al.</i> [4], <i>J Int AIDS Soc</i> . 2016
	Lamivudine monotherapy	This study suggests that 3TC monotherapy-based cART is efficacious for HBV treatment through 48 weeks in HIV/HBV coinfection when baseline HBV DNA > 20 000 IU/mL	Yijia Li <i>et al.</i> [6], <i>J Acquir Immune Defic Syndr</i> . 2016
Cardiovascular system	Cardiac diastolic dysfunction	Asymptomatic cardiac DD was observed frequently in HIV-infected subjects. HIV infection itself and zidovudine exposure were correlated with a higher prevalence of cardiac DD	Luo <i>et al.</i> [10], <i>Int J STD AIDS</i> . 2010
	Peripheral arterial disease	HIV infection itself is a risk factor of peripheral arterial disease, independent of traditional cardiovascular risk factors and cART	Ye <i>et al.</i> [14], <i>J Acquir Immune Defic Syndr</i> . 2010
	Atherosclerosis	Reduced PWV in HIV-infected Chinese patients indicates that they are more likely to develop arterial wall stiffness, possibly by atherosclerosis. A PI-free regime may be protective for the arterial wall of HIV-infected patients	Zeng Yong <i>et al.</i> [36], <i>Chin Med J</i> . 2010
	Cardiac structure and function	The prevalence of echocardiographic abnormalities was significantly higher in ART-naïve PLWH than in controls. HIV infection was significantly associated with cardiac abnormalities	Luo <i>et al.</i> [8], <i>Clin Infect Dis</i> . 2014
	CVD Risk	CVD risk factors are common but undertreated among Chinese treatment-naïve individuals with HIV	Fuping Guo <i>et al.</i> [37], <i>BMC Infect Dis</i> . 2017
	CD16 monocyte	Higher level of monocyte activation marker is associated with higher level of arterial stiffness in ART-naïve HIV-infected men	Luo <i>et al.</i> [13], <i>HIV Clin Trials</i> . 2018
Nervous system	HIV, ART, IM, CE	Cerebrovascular endothelial dysfunction associated with HIV infection may be most relevant for individuals with less traditional vascular risk, such as those with lower cholesterol	Felicia Chow <i>et al.</i> [17], <i>J Acquir Immune Defic Syndr</i> . 2017
	Cerebral vasoreactivity	In HIV populations with well-controlled infection, higher cerebral vasoreactivity, indicative of better cerebrovascular endothelial function, was associated with better performance on the MoCA	Chow <i>et al.</i> [16], <i>J Acquir Immune Defic Syndr</i> . 2018
	Efavirenz concentration	A dosage reduction of efavirenz to 400 mg daily may warrant consideration in this population, especially for those with lower body weight (< 60 kg)	Guo <i>et al.</i> [18], <i>HIV Med</i> . 2018
Kidney	TDF + PI/r	TDF + PI/r-based ART regimen resulted in greater renal function decline over 48 weeks. Renal function should be monitored especially when TDF is used in combination with PI/r	Cao <i>et al.</i> [21], <i>BMC Infect Dis</i> . 2013
	CKD	The incidence of CKD is high in Chinese HIV-infected ART-naïve patients. Traditional risk factors for renal disease, such as advancing age, HCV coinfection and higher plasma viral load, were correlated with CKD in the patient samples	Cao <i>et al.</i> [20], <i>Nephrology</i> . 2013
Skeletal system	Bone turnover and BMD	Chinese adults with HIV-1 infection have low bone turnover prior to cART as well as lower raw BMD of the lumbar spine compared with healthy controls, with further bone loss occurring following the initiation of cART	Zhang <i>et al.</i> [24], <i>BMC Musculoskelet Disord</i> . 2013
	TDF + LPV/r	Switching to TDF/3TC + LPV/r after treatment failure resulted in greater increases in BTMs than initiation with ZDV/3TC + NVP in Chinese patients with HIV. Following this change, bone resorption marker levels increased by nearly 60%	Hsieh <i>et al.</i> [27], <i>Osteoporos Int</i> . 2015
	Vitamin D-binding protein	DBP in bone loss associated with TDF-based therapy. DBP levels increase over time following initiation of TDF + 3TC + EFV among individuals with HIV	Hsieh <i>et al.</i> [28], <i>AIDS</i> . 2016

Table 1 (Continued)

System or Organ	Object	Main conclusion	Reference
Glucose	Diabetes and IFG	A high incidence of DM and IFG was detected in Chinese HIV-infected patients receiving cART, particularly those of advanced age, with hepatitis B virus coinfection or high baseline fasting glucose	Chengda <i>et al.</i> [34], <i>J Acquir Immune Defic Syndr.</i> 2015
Lipid	Adiponectin and leptin	The adiponectin level had a correlation with serum triglycerides, serum insulin concentration and HDL-C, suggesting that adiponectin may link the metabolic abnormalities and HIV-LD	Luo <i>et al.</i> [31], <i>AIDS Res Hum Retroviruses.</i> 2009
	DXA	Applying DXA to assess HIV-infected patient's body composition changes could provide objective information for physicians to prevent LD and osteoporosis	Yao <i>et al.</i> [29], <i>J Clin Densitom.</i> 2011

3TC, lamivudine; BMD, bone mineral density; BTM, bone turnover markers; cART, combination antiretroviral therapy; CE, cerebrovascular endothelial; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, vitamin D-binding protein; DD, diastolic dysfunction; DM, diabetes mellitus; DXA, dual-energy X-ray absorptiometry; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IM, Inflammatory markers; LD, lipodystrophy; LPV/r, lopinavir/ritonavir; MoCA, minimum obstruction clearance altitudes; PI, protease inhibitor; PLWH, people living with HIV; PWV, pulse wave velocity; TDF, tenofovir.

related to DD, while traditional cardiovascular risk factors such as blood pressure, diabetes, and low-density lipoprotein cholesterol were not independently associated with DD. The prevalence of left ventricular systolic dysfunction and increased left ventricular mass (ILVM) in the PLWH group was higher than that of healthy people. The multivariate logistic analysis showed that HIV was a major risk factor for DD and ILVM. Our study results suggest that HIV may trigger mechanisms that lead to cardiac dysfunction [8].

Studies have shown that heart dysfunction of PLWH is related to cART [9]. Mitochondrial toxicity of ZDV mainly exists in various tissues, including cardiomyocytes. After using ZDV for more than 12 months, the prevalence of cardiac DD increased [10]. Abacavir has been reported to increase the risk of myocardial infarction in patients; however, a 2011 meta-analysis of the Food and Drug Administration showed no statistical association between abacavir and myocardial infarction. The International Antiviral Society–USA and Department of Health and Human Services 2018 guidelines suggest avoiding abacavir (ABC)-based programmes for high CVD risk. Physicians treating patients who are already being administered medication at the risk of developing tip tortuous ventricular tachycardia should be more cautious in choosing efavirenz (EFV) and rilpivirine. The use of the protease inhibitor (PI) is associated with a variety of metabolic abnormalities, including dyslipidaemia, insulin resistance, endothelial dysfunction and CVD. Drug–drug interactions between cART and some statins and hypotensive drugs occur frequently; therefore, drug toxicity and concentration should be fully considered in the combined treatment. To be sure, the benefits of cART in reducing morbidity and mortality far outweigh the increased risk of CVD caused by cART.

Immune activation and inflammation caused by HIV may lead to cardiac dysfunction. PLWH are more likely to develop premature atherosclerosis (AS). Monocytes and monocyte-derived macrophages are cellular hallmarks in AS pathogenesis [11]. The level of neopterin can reflect the activation stage of a mononuclear/macrophage. High circulating levels of soluble tissue factors (TFs) were associated with an increased risk of subclinical AS in PLWH [12]. Mononuclear cells expressing CD16, neopterin, TFs and pulse wave velocity were significantly higher in male PLWH than in healthy controls. Elevated levels of monocyte activation markers were associated with high levels of AS in male PLWH who were receiving cART [13]. Conversely, oestrogen has a significant protective effect on AS; women affected by HIV are much less likely to develop AS than men of the same age. HIV infection itself is a risk factor for peripheral artery disease, independent of traditional cardiovascular risk factors and cART; therefore, treating a potential HIV infection may prevent the progression of AS [14].

We suggest that CVD risk assessment could be carried out for PLWH, and treatment and intervention should be considered as part of medical care. cART with small influence on lipid metabolism was selected as far as possible. In changing the cART regimen, the relationship between efficacy and adverse reactions should be weighed.

### Dementia is associated with changes in cerebrovascular elasticity

Despite the extensive use of cART, cognitive impairment remains prevalent in PLWH, potentially due to, in part, damage to small blood vessels in the brain [15]. Cerebrovascular endothelial dysfunction may be an independent factor, leading to cognitive impairment in PLWH. A

simple auxiliary examination to determine cerebrovascular endothelial function may identify an individual's risk of cognitive dysfunction at an early stage and reduce dementia's irreversible loss. Cerebral vasoreactivity is an index of cerebrovascular endothelial function that can be non-invasively assessed by transcranial Doppler ultrasound and is associated with both cerebral small vessel disease and severe AS, which are two common stroke mechanisms in HIV infection. By utilizing the breath-holding challenge to measure cerebral vasoreactivity, poor cerebral vasoreactivity indicates poor cerebrovascular endothelial function. We concluded that women, a longer duration of HIV diagnosis, and higher high-sensitivity C-reactive protein were associated with poorer cognitive performance [16]. PLWH with low total cholesterol who received cART and had virological inhibition had poorer cerebral vasoreactivity than non-HIV-infected controls [17]. With increase in age, traditional vascular risk factors, such as dyslipidaemia, become increasingly common, which may play a more important role in the overall stroke risk, masking the impact of HIV infection. The corollary that should be emphasized is that PLWH without traditional vascular risk factors (such as elevated total cholesterol) may still have an increased cerebrovascular risk compared with uninfected individuals.

In addition to the direct effects of the virus, the effects of cART on the central nervous system also need to be evaluated. We found that lopinavir/ritonavir (LPV/r) use was associated with reduced cerebral vasoreactivity in 3TC combined with TDF or ZDV compared with EFV [17]. The CACT data showed that endothelial dysfunction associated with PI use might extend from the systemic vascular system to the brain and provide a possible mechanism to explain the higher risk of non-haemorrhagic stroke events associated with PI exposure in HIV-infected individuals and the pathology of cerebral small-vessel disease [17]. Although ZDV and NVP are no longer first-line recommended drugs, some patients in China still maintain the antiviral treatment of 3TC + ZDV + NVP. ZDV and NVP both have good cerebrospinal fluid permeability. For PLWH who have progressive multifocal leukoencephalopathy, the cART regimen could considerably be adjusted to contain ZDV, NVP or dolutegravir (DTG). The use of DTG should also refer to the patient's economic purchasing ability.

Efavirenz-based cART was included in China's first-line recommended antiviral therapy in 2011. A meta-analysis published in July 2014 in the *Annals of Internal Medicine* found that suicidal ideation and attempts were twice as common in the EFV group as in other cART regimens. The rapid increase in the rate of change and withdrawal of EFV during long-term follow-up may also be due to

patients' psychological adverse reactions, which is the main reason for the decline in the long-term treatment effect. The CACT data showed that patients were grouped according to their body weight with 60 kg as the cut-off value, and the blood concentration of EFV in the low-weight group was significantly higher than that in the high-weight group. Plasma EFV concentration significantly negatively correlated with body weight and was higher in patients with low body weight [18]. Chinese patients with AIDS have higher concentrations of EFV. We further recommend that Chinese patients with AIDS, especially those of low weight, be given a 400 mg dose of EFV, which can significantly reduce neurological adverse reactions, thus updating this decision in the Chinese guidelines for diagnosis and treatment of HIV/AIDS 2018 [1].

### High incidence of chronic kidney disease among PLWH

Chronic kidney disease (CKD) is a frequent complication of HIV. The incidence of CKD in PLWH has attracted increased attention in recent years. Proteinuria, decreased creatinine clearance and glomerular filtration rate (GFR) in PLWH are associated with a rapid progression and death from AIDS [19]. CKD prevalence and proteinuria in PLWH in China were 16.1% and 12.2%, respectively, higher than in healthy people. A study of PLWH in China found that CKD was significantly correlated with age, hypertension, HIV/HCV coinfection and HIV viral load  $\geq 100\ 000$  copies/mL [20]. HCV may cause kidney disease and its antibodies are deposited in the glomerular basement membrane, potentially inducing membranoproliferative glomerulonephritis, an immune-complex disease, which leads to kidney damage. Some studies have confirmed that HIV replication in renal cells is a prerequisite for the occurrence of disease, and circulating viral RNA is associated with the progression of kidney disease; therefore, effectively inhibiting viral replication can improve kidney function and prolong kidney survival time [21,22]. The potential nephrotoxicity of antiviral drugs can either cause or accelerate the development of CKD. The mechanism of renal injury caused by TDF is the mitochondrial dysfunction of proximal renal tubules caused by drug accumulation, which leads to proximal renal tubule injury and dysfunction. Patients who underwent treatment, including with TDF, had a substantially lower GFR [23]; although this change returned to normal in some patients after withdrawal, TDF should be avoided as much as possible in elderly and renal insufficiency patients. Discontinuation of TDF is recommended in

patients with estimated GFR  $\leq 60$  mL/min/1.73 m<sup>2</sup> or a decline of  $> 25\%$  from baseline [22]. Early identification of CKD and diagnosis of its underlying cause are crucial when treating PLWH. Management of PLWH with CKD comorbidity should also include blood pressure, metabolic, and potentially nephrotoxic, drug management, infection control and renal function assessment. Those with potentially impaired kidney function and those who initiated the administration of potentially toxic medication may benefit from more frequent evaluations.

## Effects of HIV and cART on bone metabolism

People living with HIV are prone to the clinical characteristics of low bone mass and high bone turnover rate due to the virus infection itself and cART. Different ethnic groups differ in fracture rate, bone density and bone structure. We found that, compared with healthy individuals, Chinese HIV-1 patients had lower bone conversion rate and lumbar primordial bone mineral density (BMD) before cART, with further bone loss after cART initiation. BMD of the lumbar spine, femoral neck and total hip in PLWH decreased significantly within 48 weeks of cART, remained stable at 48–96 weeks, and the annual percentage decline ranged from 1.78% to 3.28%. Levels of collagen type 1 cross-linked C-telopeptide ( $\beta$ -CTX) and procollagen type 1 N-terminal propeptide (P1NP) in PLWH were lower at baseline, and both were elevated within 48 weeks of cART and remained stable during the following 48 weeks. Patients with HIV had a higher baseline parathyroid hormone (PTH) and a significant increase within 96 weeks of cART. There was no statistically significant reduction in 25-OH vitamin D (25OHD) [24]. The resulting vitamin D deficiency with secondary hyperparathyroidism is common in this population.

The BMD of AIDS patients decreased by 2–6% in the first 2 years after initiation of cART therapy, similar to a 2-year menopause, and the incidence of fracture in this group was 30–70% higher than that in non-infected persons. The effects of TDF on bone may be related to the direct effects on bone cells or the indirect effects of secondary hyperparathyroidism and failure of calcium phosphate homeostasis leading to inadequate bone mineralization [25]. Compared with other nucleoside reverse transcriptase inhibitors, BMD had a 1–2% greater decline in patients undergoing the TDF regimen [26].

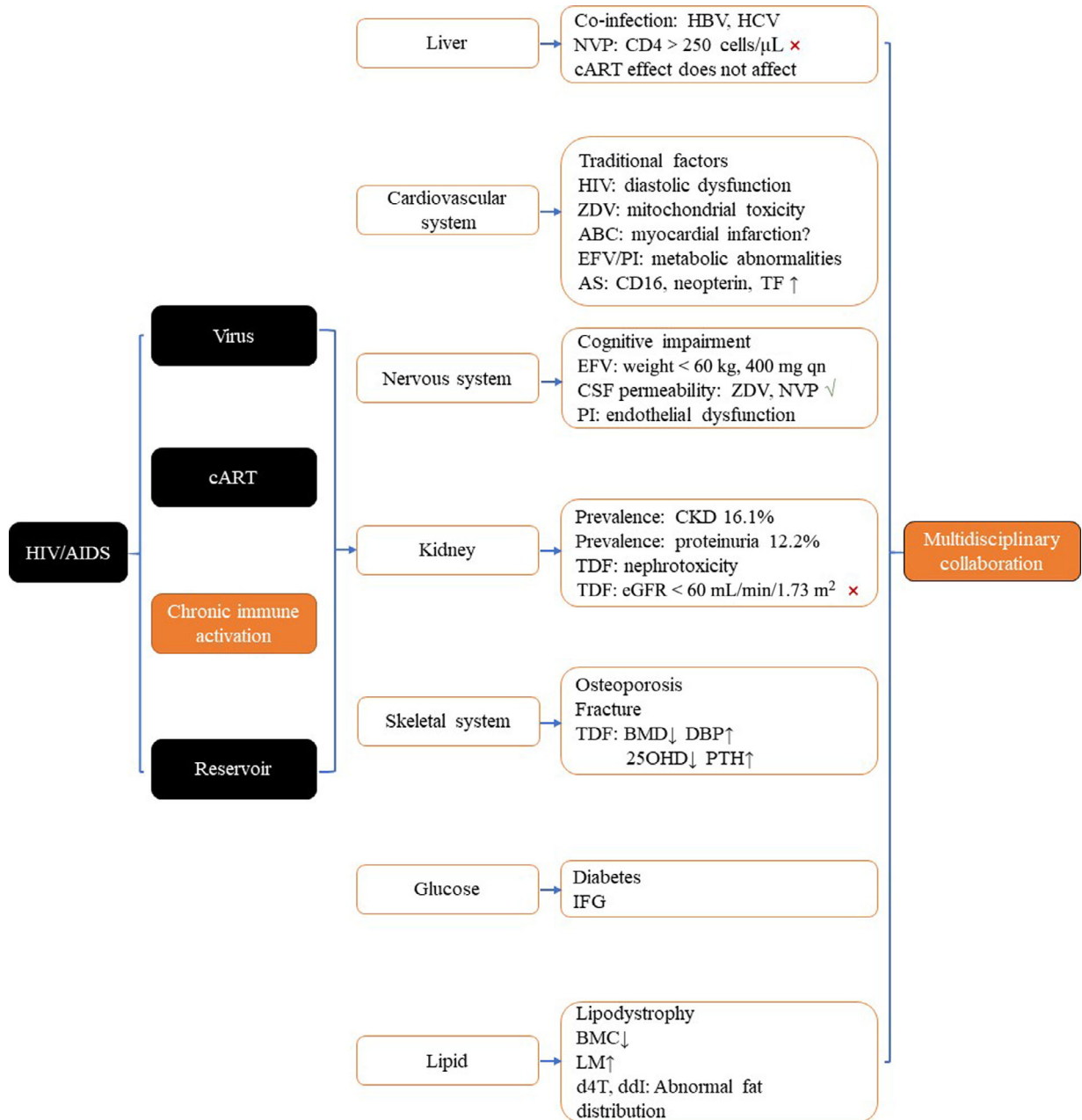
In our study of the treatment-experiment cohort of PLWH in China, we found that, as assessed by CTX, bone resorption was significantly increased in patients undergoing the TDF + LPV/ r regimen [27]. The PI is

potentially caused by bone loss through either the activation of osteoclasts or the inhibition of osteoblasts [26]. However, we believed that TDF was a major driver of the observed increase in bone resorption. In the treatment-naïve cohort, we found that exposure to TDF-based cART may lead to increasing vitamin D binding protein levels, decreased bioavailability of 25OHD, and increased iPTH compensation [28]. Supplementation with vitamin D may alleviate bone loss associated with the use of ART such as TDF. This is a prospective study being conducted by the CACT to untangle the toxicity of osteoporosis caused by long-term treatment with TDF. The number of PLWH receiving TDF treatment is still increasing in China; however, diagnosis and treatment of osteoporosis and fractures still vary in different regions. Therefore, it is increasingly important to include TDF-based treatment in future studies to assess the impact of cART on bone disease in HIV-infected Chinese patients.

HIV infection and the use of TDF are high-risk factors for fracture; more attention should be given to bone health in these patients. For patients with bone disorders, TDF should be avoided, and ABC can be considered to either replace TDF or a simplified treatment regimen. Moreover, a comprehensive assessment of both bone mass and bone metabolism was conducted in conjunction with endocrinologists to intervene and improve the bone health of patients with AIDS.

## Dual-energy X-ray absorptiometry (DXA) was recommended to assess PLWH with clinical lipodystrophy

Lipodystrophy (LD) is commonly used to describe a common fat redistribution syndrome in PLWH, especially in patients receiving long-term cART. The abnormal distribution of fat in the whole body is the decrease of fat in the face, upper limbs, lower limbs and buttocks and/or the accumulation of fat in the abdomen, neck and back. The incidence of LD among PLWH varies according to race. Sex differences make men more likely to experience fat atrophy and women more likely to experience fat accumulation. Chinese male PLWH and LD comorbidity frequently showed a significant decrease in peripheral and central fat, decreased bone mineral content (BMC), and increased lean mass (LM) [29]. Early detection and diagnosis of LD is important for PLWH; LD not only affects the appearance of the patient but may reduce the effectiveness of ART [30]. The fat mass (FM) of Chinese male PLWH was negatively correlated with the duration of HIV infection and the duration of cART. FM was positively correlated with body weight and BMC content and



**Fig 1** Multisystem complications of HIV infection. cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; NVP, nevirapine; ZDV, zidovudine; ABC, abacavir; EFV, efavirenz; PI, protease inhibitor; AS, atherosclerosis; TF, tissue factors; CSF, cerebrospinal fluid; CKD, chronic kidney disease; TDF, tenofovir; GFR, glomerular filtration rate; BMD, bone mineral density; DBP, vitamin D-binding protein; 25OHD, 25-OH vitamin D; PTH, parathyroid hormone; IFG, impaired fasting glucose; BMC, bone mineral content; LM, lean mass; d4T, stavudine; ddI, didanosine. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

negatively correlated with LM content. HIV-infected males with LD have lower body and regional FMs and lumbar spine BMD compared with non-LD patients, and their body, trunk and leg BMC was also lower than those in healthy people [29]. We recommend that DXA measurement be used as an auxiliary objective examination

to evaluate the changes of body composition in PLWH, and the indices of FM, LM, BMC and BMD could be measured for a comprehensive evaluation.

The d4T, considered as a HIV-LD-inducing medication, was discontinued due to severe abnormal fat distribution and atrophy. In patients who previously used D4T and

didanosine as the backbone ART regimen, baseline CD4 cell levels and adiponectin levels were lower in HIV-LD patients than in HIV-NLD patients. The results showed that both the adiponectin concentration at baseline and the adiponectin change rate at 18 months were risk factors for the development of HIV-LD [31]. The decrease of adiponectin may be related to the increased expression of the tumour necrosis factor (TNF)- $\alpha$  gene in the subcutaneous fat, which inhibits the expression of the adiponectin gene and secretion of fat cells *in vitro* [32].

## Incidence and risk factors of diabetes/ impaired fasting glucose tolerance in PLWH

Elevated plasma glucose is involved in myocardial infarction and stroke, and the incidence of myocardial infarction and stroke is increased among PLWH; therefore, diabetes is a particular concern in an HIV infection [33]. The incidence of diabetes and impaired fasting glucose among PLWH receiving cART in China was higher than that of healthy people, at 2.62 and 35.64 per 100 person-years, respectively. It is important for clinicians to note that there may be an increased risk of glycaemic disorders among PLWH in China, especially those who are older, have HIV/HBV coinfection, or have high baseline fasting glucose levels [34].

## Conclusion

HIV's direct damage to human cells, chronic abnormal inflammatory activation after HIV infection, long-term drug side effects caused by cART and persistent reservoirs cause systemic complications in PLWH (Fig. 1). AIDS is a chronic inflammatory disease, and the continuous activation of the immune system is one of the most important immunopathological changes of HIV/AIDS throughout the course of the disease. Treating the chronic abnormal immune activation of AIDS will certainly improve the long-term prognosis of patients. Regarding the suppression of inflammation and immune activation, there is currently no effective method. Combining clinical practice, we preliminarily found that *Tripterygium wilfordii* can suppress immune activation and improve immune reconstruction, providing a new direction for the treatment of AIDS. Nevertheless, the management of the complications of HIV infection will play a major part in improving the survival treatment and prognosis of patients in future. The joint participation of doctors from different departments of general hospitals in the management of comorbidities is the main theme for future improvement of quality of life and prognosis for PLWH.

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