

Appendix 1

1. Diagnostic and inclusion criteria

a. Inclusion criteria for HIV/AIDS and HIV/AIDS-INR

The inclusion criteria for HIV/AIDS and the Western medical diagnostic criteria for HIV/AIDS-INR were derived from the "HIV/AIDS Treatment Guidelines (2018 Edition) published by the Chinese Medical Association AIDS Specialty Group and Infectious Diseases Branch.

Diagnosis is made when one of the following conditions is met:

- i. positive HIV antibody screening test and positive HIV supplementation test (positive antibody supplementation test or positive qualitative nucleic acid test or quantitative nucleic acid >5000 copies/mL);
- ii. positive HIV isolation test.

The following HIV/AIDS-INR diagnostic criteria were derived from the Expert Consensus on Collaborative Treatment of HIV/AIDS, Immune Non-Responders issued by the AIDS Prevention and Control Branch of the Chinese Academy of Traditional Chinese Medicine:

- i. meeting the diagnostic criteria of HIV/AIDS;
- ii. CD4+ < 300/μL or CD4+ growth rate less than 20% compared to baseline;
- iii. HIV-RNA < 50 copies/ml for more than 18 months.

All patients enrolled were required to meet the above HIV/AIDS-INR diagnostic criteria as well the following criteria:

- i: between the ages of 18 and 65 years;
- ii: HAART treatment duration of more than 2 years and plasma HIV load < 50 copies/mL for more than 18 months;
- iii: signed informed consent for participation.

b. Diagnosis criteria for LSD syndromes of HIV/AIDS-INR

Diagnostic criteria for HIV/AIDS-LSD syndrome refer to the Chinese Medicine Treatment Protocol for Adults with AIDS (2016 version) issued by the State Administration of Traditional Chinese Medicine

The primary symptoms are as follows:

- i: poor complexion, fatigue, low voice, and lazy speech;
- ii: shortness of breath and asthma, cough with thin sputum, and prolonged cough;
- iii: loss of appetite, poor appetite, bloating, and loose stools.

The secondary symptoms are as follows:

- i: pale tongue with white smooth coating;
- ii: weak pulse.

Any patient meeting 1 of the following criteria could be diagnosed as a HIV/AIDS-INR LSD.

- i: all the primary symptoms present;
- ii: primary symptoms ii and iii present;
- iii: primary symptoms ii and iii and at least 1 of the secondary symptoms present.

c. Diagnosis criteria for NS of HIV/AIDS-INR

None syndrome (NS) refers meeting the HIV/AIDS diagnostic criteria of Western medicine but with a syndrome score of zero as and no obvious symptoms related to the tongue or pulse.

2. Exclusion criteria

Participants who met the inclusion criteria but had any 1 of the following were excluded from the study:

- i: uncontrolled, severe opportunistic infections;
- ii: administration of immunomodulatory agents within 1 month prior to enrollment;
- iii: in a pregnant or lactating state;
- iiii: coinfection with hepatitis C virus or hepatitis D virus;
- iiiii: combined with malignancy or cirrhosis;
- iiiii: with severe allergies or allergies to certain herbal ingredients.

3. Clinical evaluation of YDSK and NS patients

Table S1 Clinical evaluation of LSD and NS patients

Projects	LSD (n=9)	NS (n=10)	Control (n=10)	P value
Gender (female/male)	4/5	6/4	4/6	
Age (years)	(40.22±5.19)	(38.0±6.32)	(36.3±9.89)	0.517
HAART hours (months)	(48.22±28.40)	(59.10±24.19)		0.380
Viral load (cp/mL)	(17.78±21.08)	(3.20±10.12)		0.063
CD4 (cells/ μ L)	(176.11±79.23)	(166.10±40.37)		0.729
Erythrocyte (10^{12} /L)	(4.14±0.39)	(4.21±1.12)		0.288
Hemoglobin (g/L)	(142.44±14.36)	(147.60±17.61)		0.497
Leukocyte (10^9 /L)	(6.04±2.46)	(7.38±3.54)		0.540
Absolute neutrophil count (10^9 /L)	(3.79±2.13)	(4.92±2.98)		0.462
Absolute lymphocyte count (10^9 /L)	(1.71±0.39)	(1.78±0.74)		0.825
Blood platelet (10^9 /L)	(189.78±41.04)	(261.90±110.63)		0.083
Alanine aminotransferase (U/L)	(33.37±13.27)	(23.36±8.80)		0.067
Aspartate aminotransferase (U/L)	(33.96±7.67)	(26.91±11.03)		0.045
Gamma-glutamyl transpeptidase (U/L)	(53.70±32.53)	(53.42±29.61)		0.985
Blood urea nitrogen (mmol/L)	(4.88±1.77)	(4.75±2.09)		0.744
Serum creatinine (μ mol/L)	(74.49±14.60)	(75.82±12.32)		0.832

Data are presented as the mean \pm standard deviation. YDSK, Yang deficiency of spleen and kidney; LSD, lung and spleen deficiency; NS, nonsyndromic; HAART, highly active antiretroviral therapy.

4. Clinical information of participants for ELISA validation

Table S2 Clinical information of participants for ELISA validation

Projects	LSD (n=10)	Control (n=10)
Gender (female /male)	4/6	3/7
Age (years)	(40.60±6.70)	(25.90±2.13)
HAART hours (months)	(48.60±24.28)	
Viral load (cp/mL)	(4.00±12.65)	
CD4 (cells/μL)	(233.40±52.10)	
Erythrocyte (10 ¹² /L)	(4.56±0.95)	
Hemoglobin (g/L)	(150.10±26.08)	
Leukocyte (10 ⁹ /L)	(5.63±1.77)	
Absolute neutrophil count (10 ⁹ /L)	(3.08±1.30)	
Absolute lymphocyte count (10 ⁹ /L)	(2.02±0.58)	
Blood platelet (10 ⁹ /L)	(186.30±63.69)	
Alanine aminotransferase (U/L)	(45.31±19.26)	
Aspartate aminotransferase (U/L)	(45.60±14.24)	
Gamma-glutamyl transpeptidase (U/L)	(43.21±22.34)	
Blood urea nitrogen (mmol/L)	(4.67±1.88)	
Serum creatinine (μmol/L)	(74.49±13.29)	

Data are presented as mean ± standard deviation. LSD, lung and spleen deficiency HAART, highly active antiretroviral therapy.

5. Volcano map of DEPs

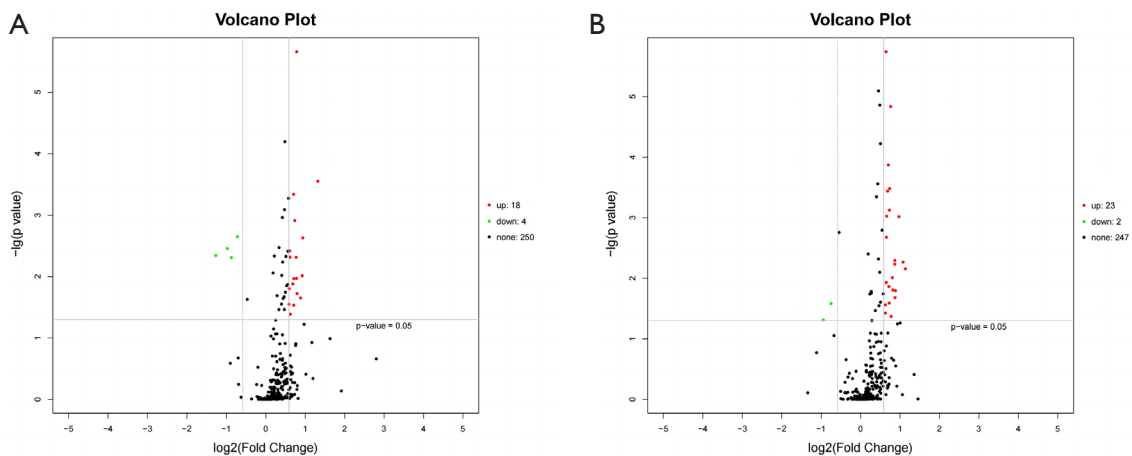


Figure S1 (A) Volcano plot of DEPs between the LSD-INR and HC groups. (B) Volcano plot of the DEPs between the NS-INR and HC groups. DEP, differentially expressed protein; LSD, lung and spleen deficiency; INR, immunological nonresponder; HC, healthy control; NS, nonsyndromic.