(5R)-5-hydroxytriptolide for HIV immunological non-responders receiving ART: A randomized, double-blinded, placebo-controlled phase II study

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Background

Around 20–30% of treated patients with HIV fail to achieve optimal immune reconstitution despite effective antiretroviral therapy (ART), and remain at greater risk of morbidity and mortality. Therapeutic approaches to HIV-suppressed immunological non-responders (INRs) remain unsettled. We previously reported efficacy of Chinese herbal Tripterygium wilfordii Hook F in INRs. Its derivative (5R)-5-hydroxytriptolide (LLDT-8) on CD4 T cell recovery was assessed.

Figure 1. Chinese herbal Tripterygium wilfordii Hook F

Methods

The phase II, double-blind, randomized, placebo-controlled trial was conducted in adults patients with long-term suppressed HIV infection and suboptimal CD4 recovery, at nine hospitals in China. The patients were 1:1:1 assigned to receive oral LLDT-8 0.5 mg or 1 mg daily, or placebo combined with ART for 48 weeks. All study staff and participants were masked. The primary endpoints include change of CD4 T cell counts and inflammatory markers at week 48.

- *This study is registered on ClinicalTrials.gov (NCT04084444) and Chinese Clinical Trial Register (CTR20191397).*

Table 1: Participating center and investigators

No	Centers	Investigator
01	Peking Union Medical College Hospital, Chinese Academy of Medical Sciences (PUMCH, CAMS, Beijing)	Li, Taisheng
02	Beijing YouAn Hospital, Capital Medical University (Beijing)	Sun, Lijun
03	Beijing DiTan Hospital, Capital Medical University (Beijing)	Zhang, Tong
04	The Second Hospital of Nanjing (Nanjing, Jiangsu Province)	Wei, Hongxia
05	The First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou, Zhejiang Province)	Zhu, Biao
06	The First Hospital of Changsha (Changsha, Hunan Province)	Wang, Min
07	Tianjin Second People's Hospital (Tianjin)	Ma, Ping
08	Yunnan Provincial Infectious Disease Hospital (Kunming, Yunan Province)	Wang, Xicheng
09	Affiliated Hangzhou Xixi Hospital, College of Medicine, Zhejiang University (Hangzhou, Zhejiang Province)	Yu, Jianhua

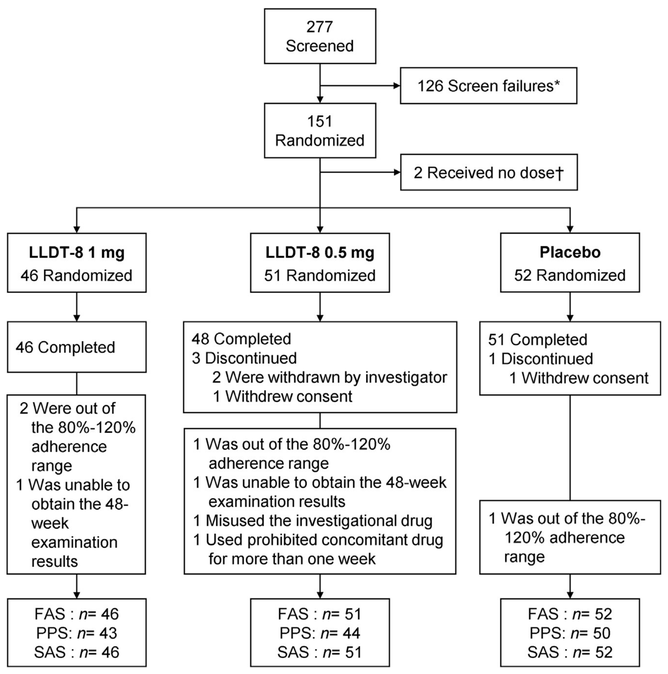

Figure. 2: Flow diagram for study design and enrollment. * Of the 126 participants who were not randomly assigned in initial screening for study eligibility, 59 did not meet inclusion criteria, 52 met the exclusion criteria, and 15 had other reasons. † The two participants received no drug for being confirmed with CD4+ T cell >350 cells/mm^3 at screening (359 and 436 cells/mm^3 separately), which was against the inclusion criteria.

Table 2. Characteristics of the Participants at Baseline, According to Full Analysis Set*

Characteristics	Total (N=149)	LLDT-8 1 mg (N=46)	LLDT-8 0·5 mg (N=51)	Placebo (N=52)
Male sex — no. (%)	145 (97.3)	46 (100)	48 (94.1)	51 (98.1)
Age, median (range) — yr	41 (22-64)	41 (28-64)	41 (26-61)	44 (22-64)
Age group — no. (%)				
18-45 yr	91 (61.1)	29 (63.0)	35 (68.6)	27 (51.9)
45-65 yr	58 (38.9)	17 (37.0)	16 (31.4)	25 (48.1)
Ethnicity Han — no. (%)	142 (95.3)	44 (95.7)	48 (94.1)	50 (96.2)
BMI — kg/m^2	22.3 ± 2.5	22.1 ± 2.2	22.5 ± 2.9	22.2 ± 2.4
ART duration, median (range) — yr	6.1 (4.1-14.9)	6.1 (4.1-11.7)	6·1 (4.1-14.9)	6.0 (4.2-10.7)
ART regimens — no. (%)				
NNRTI-based	105 (70·5)	31 (67·4)	39 (76·5)	35 (67·3)
TDF+3TC+EFV	68 (45·6)	19 (41·3)	27 (52·9)	22 (42·3)
PI/r-based	27 (18·1)	12(26·1)	6 (11·8)	9 (17·3)
INSTI-based	17 (11·4)	3 (6·5)	6 (11·8)	8 (15·4)
CD4 count, median (range) — cells/mm^3	248 (18-347)	249 (18-343)	243 (87-347)	249 (119-341)
CD4 stratification— no. (%)				
< 200 cells/mm^3	38 (25.5)	10 (21.7)	15 (29.4)	13 (25.0)
≥ 200 cells/mm^3	111 (74.5)	36 (78.3)	36 (70.6)	39 (75.0)
CD8 count, median (range) — cells/mm^3	518 (134-1611)	527 (134-1196)	495 (177-1383)	538 (255-1161)
CD4/CD8 ratio, median (range)	0.45 (0.10-1.61)	0.45 (0.10-1.61)	0.47 (0.21-1.27)	0.45 (0.15-1.26)

* The analysis set for participants who underwent randomization in this study. Percentages may not total 100 because of rounding. Plus–minus values are means ± SD. BMI denotes body mass index; SD, standard deviation; cART, combined antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; TDF, tenofovir; 3TC, lamivudine; EFV, efavirenz; PI/r, ritonavir-boosted protease inhibitor; INSTI, integrase strand transfer inhibitor.

Results

- A total of 149 patients were enrolled from Aug 30, 2019 and randomly allocated to receiving LLDT-8 0.5 mg daily (LT8, n = 51), 1 mg daily (HT8, n = 46), or placebo (PL, n = 52). The median baseline CD4 count was 248 cells/mm3, comparable among three groups. LLDT-8 was well-tolerated in all participants.
- At 48 weeks, change of CD4 counts was 49 cells/mm^3 in LT8 group (95% confidence interval [CI]: 30, 68), 63 cells/mm^3 in HT8 group (95% CI: 41, 85), compared to 32 cells/mm^3 in placebo group (95% CI: 13, 51). LLDT-8 1 mg daily significantly increased CD4 count compared to placebo (p = 0.036), especially in participants over 45 years.
- The mean change of serum interferon-γ-induced protein 10 was −72.1 mg/L (95% CI −97.7, −46.5) in HT8 group at 48 weeks, markedly decreased compared to −22.8 mg/L (95% CI −47.1, 1.5, p = 0.007) in placebo group.
- Treatment emergent adverse events (TEAEs) were reported in 41 of 46 (89.1%) participants in HT8 group, 43 of 51 (84.3%) in LT8, and 42 of 52 (80.7%) in PL group. No drug-related SAEs were reported.

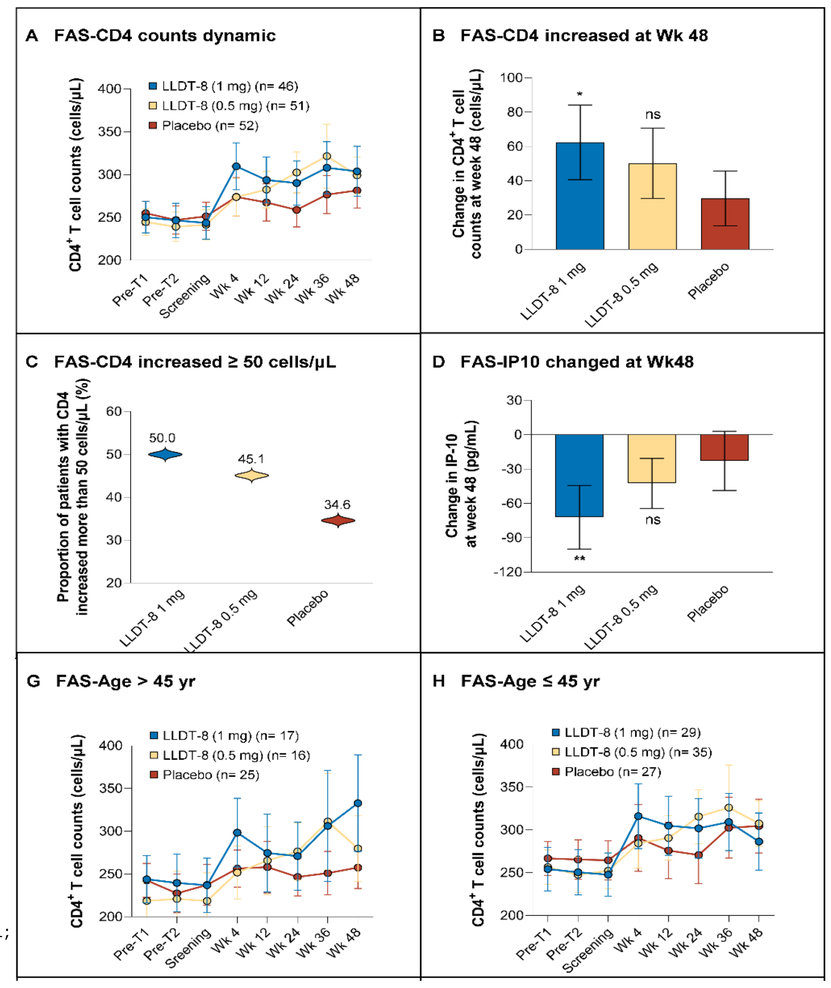

Figure 3: The CD4+ T-cell recovery and cytokine changes among FAS population. Pre-screening timepoints 1 and 2 were within one year before the screening. Data were shown and exhibited as mean and 95% CI. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001; ns, not significant when compared to the placebo group.

Conclusion

LLDT-8 enhanced CD4 recovery and alleviated inflammation in long-term suppressed INRs, providing them a potential therapeutic option for HIV INR patients. The benefit was superior with LLDT-8 dosage 1 mg daily, and in older participants. Future larger size of clinical studies and pharmacological research into underlying mechanisms are needed to better understand its effectiveness.

Acknowledgement

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