Anti-PD-L1 antibody ASC22 in combination with chidamide potentiates HIV latency reversal and immune function from ART-suppressed individuals: a single center, single-arm, phase II study

NO. AS-IAS-2023-05701

***Correspondence: Jun Chen (qtchenjun@163.com); Hongzhou Lu (luhongzhou@fudan.edu.cn)**

L. Wu [1, 2], Z. Zheng [1, 3], J. Xun [1, 4], L. Liu [1], J. Wang [1], R. Zhang [1], M. Sun [1], H. Lu [5], J. Chen [1]

1.Department of Infectious Diseases and Immunology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China, 2.Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China, 3.Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai, China, 4.State Key Laboratory of Genetic Engineering and Engineering Research Center of Gene Technology, Ministry of Education, Institute of Genetics, School of Life Sciences, Fudan University, Shanghai, China, 5.Department of Infectious Diseases and Nursing Research Institution, National Clinical Research Center for Infectious Diseases, The Third People's Hospital of Shenzhen, Shenzhen, China General

Background. The combination of chidamide, an HIV latency reversal agent, and an anti-PD-L1 antibody ASC22 , which potentially boosts HIV-specific immunity, may serve as a "shock and kill" functional cure treatment strategy for HIV.

Methods. People living with HIV who had achieved virological suppression were enrolled to receive a subcutaneous injection of ASC22 (1mg/kg) every four weeks for three cycles. Chidamide (10 mg) was administered orally twice weekly for 12 weeks while maintaining antiretroviral therapy. Participants were followed up for 24 weeks and measured the changes in the levels of cell-associated (CA) HIV RNA, plasma HIV RNA, total and integrated HIV DNA and HIV-specific CD8+ T cell function (NCT05129189).

Results. There was a significant increase in CA HIV RNA at week 8 and week 12 compared to the baseline, with an average rise of 4.27-fold and 3.41-fold, respectively (P=0.001, P=0.006). The HIV CA RNA to total DNA ratios also showed the same trend (P=0.038, P=0.017, respectively). However, these markers returned to the baseline after discontinuing ASC22 and chidamide. In contrast, the total HIV DNA and integrated HIV DNA were only transiently increased at week 4 , respectively (P=0.001, P=0.003). Significant increases in the proportions of effector memory $CD4^+$ and $CD8^+$ T cells (T_{EM}) were observed from baseline to week 24 (P=0.003 and P<0.001, respectively). The functional capacity of HIV Gag- and Pol-specific $CD8^+$ T cells did not succeed in enhancing with combination treatment. However, At week 8, a significant negative correlation was observed between the secretion of IFN-γ and TNF-α by HIV Gag-specific $CD8^+$ T_{EM} cells in the T cell function improved group and alterations in integrated DNA (P=0.042, R^2=-0.892 and P=0.034, R^2=-0.792, respectively). Nine adverse events were deemed drug-related, all of which were graded 1 and resolved spontaneously.

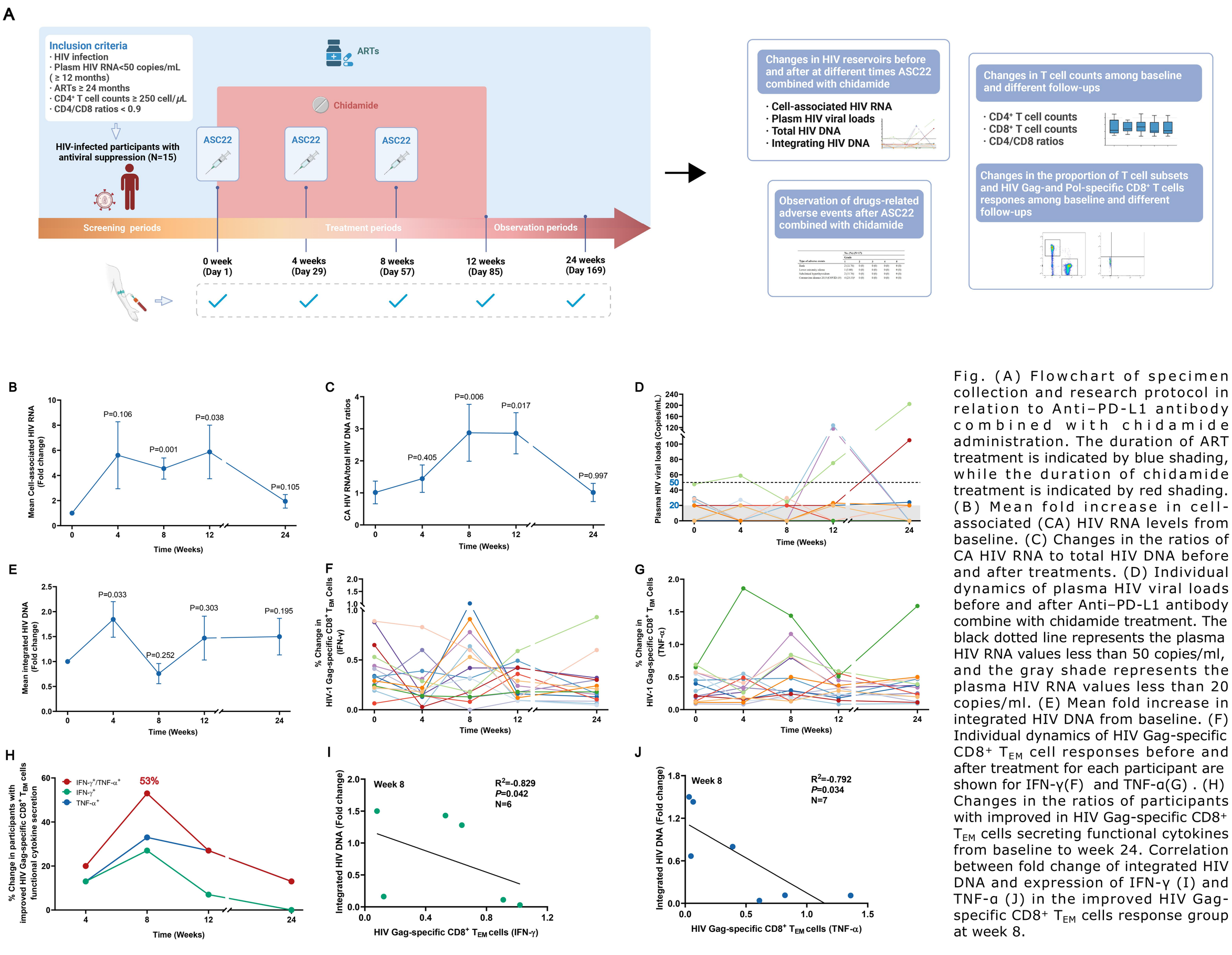

Fig. (A) Flowchart of specimen collection and research protocol in relation to Anti–PD-L1 antibody combined with chidamide administration. The duration of ART treatment is indicated by blue shading, while the duration of chidamide treatment is indicated by red shading. (B) Mean fold increase in cell-associated (CA) HIV RNA levels from baseline. (C) Changes in the ratios of CA HIV RNA to total HIV DNA before and after treatments. (D) Individual dynamics of plasma HIV viral loads before and after Anti–PD-L1 antibody combine with chidamide treatment. The black dotted line represents the plasma HIV RNA values less than 50 copies/ml, and the gray shade represents the plasma HIV RNA values less than 20 copies/ml. (E) Mean fold increase in integrated HIV DNA from baseline. (F) Individual dynamics of HIV Gag-specific $CD8^+$ T_{EM} cell responses before and after treatment for each participant are shown for IFN-γ(F) and TNF-α(G) . (H) Changes in the ratios of participants with improved in HIV Gag-specific $CD8^+$ T_{EM} cells secreting functional cytokines from baseline to week 24. Correlation between fold change of integrated HIV DNA and expression of IFN-γ (I) and TNF-α (J) in the improved HIV Gag-specific $CD8^+$ T_{EM} cells response group at week 8.

Conclusion. Combination treatment with ASC22 and chidamide is well tolerated, which effectively activated latent HIV reservoirs. This strategy reduces the size of the HIV reservoir only in populations with enhanced T-cell functionality. Further investigations are warranted to boost the killing function.