Pomalidomide as an immune-enhancing agent for the control of HIV

(PEACH)

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Background: Antiretroviral therapy (ART) effectively suppresses HIV replication and prevents the development of AIDS, but lifelong treatment is required, and this is associated with a risk of long-term toxicities, stigmatization and drug resistance. Persistence of HIV in latently infected $CD4^+$ T-cells remains a major impediment to eradication. Other obstacles include immune exhaustion and the dysfunctional immune responses associated with chronic HIV infection. A key component of future HIV cure strategies could therefore be the use of immune-modifying drugs to re-invigorate dysfunctional HIV specific immune responses.

Preliminary data: Pomalidomide is an immune-modulating drug that is well-tolerated and licensed for the treatment of refractory multiple myeloma, and Kaposi sarcoma. Pre-clinical data from our lab has shown that pomalidomide reduced the frequency of dysfunctional CD56-CD16+ NK cells in samples from people living with HIV (PLWH) treated *ex vivo*, whilst increasing NK cell polyfunctionality. This profile supported greater killing of HIV-infected cells. Furthermore, pomalidomide drove a substantial expansion of HIV-specific $CD8^+$ T-cells and markedly increased CD8+ T-cell-mediated HIV-specific lysis *ex vivo*. Collectively, the pre-clinical data demonstrates that pomalidomide enhances anti-HIV immunity *ex vivo* and provides a compelling rationale for the evaluation of pomalidomide as a therapeutic agent to support immune control of HIV.

Methods: The study is a phase I/IIb clinical trial of pomalidomide in otherwise healthy PLWH on ART (NCT06660498). 32 participants will be randomised 1:1 to receive pomalidomide 2 mg or placebo for three treatment cycles, each consisting of 21 days on and a minimum of 7 days off. In phase I, participants will receive treatment cycle I while on suppressive ART. In phase II, participants will receive treatment cycle II and III in the setting of an analytical treatment interruption (ATI). Primary outcomes are safety and time to viral rebound. Secondary outcomes are rebound viral kinetics during the ATI, HIV-specific T-cell responses and changes in the intact and inducible HIV reservoir.

Conclusion: This clinical trial will inform the use of pomalidomide as an immune enhancing agent to reinvigorate anti-HIV immunity as part of HIV curative strategies, and may support immunological control of HIV in the absence of ART.