Impact of High Dose Vitamin D_3 Supplementation on Innate Immunity and Antimicrobial Functions in Adolescents with HIV-1 on ART

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1 Introduction

- Vitamin D (Vit.D) deficiency is highly prevalent in the HIV-1 cohort and is associated with increased risk to microbial infections e.g. *Mycobacterium tuberculosis*
- Bioactive Vit.D (Vit.D_3) improves innate immunity against microbial pathogens by upregulating genes and pathways for antimicrobial peptides which highlights a niche for host-directed therapy
- Given the overlapping risk for chronic HIV-1 disease outcomes with those observed in Vit.D deficiency, there is a need to clarify the clinical importance of Vit.D supplementation in the HIV-1 cohort
- In VITALITY, an ongoing placebo-controlled phase 3 clinical trial where HIV-1-infected adolescents on ART in Zambia and Zimbabwe are receiving weekly high dose vitamin D_3 (20,000IU) and daily calcium carbonate (500mg) supplementation to assess impact on musculoskeletal health and immunopathology;
- **Our sub-study will assess the effects of vitamin D_3 supplementation on neutrophils and monocyte activation and polarization, antimicrobial killing and modulation of chemo/cytokine production**

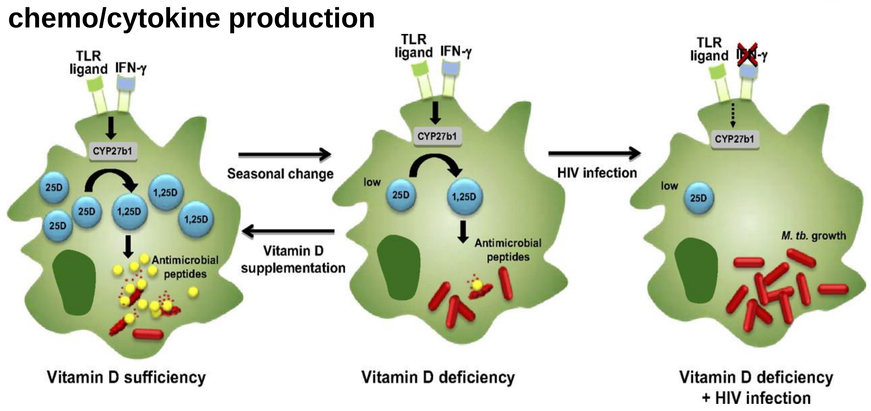


Figure 1: Vitamin D deficiency and risk of bacterial infections in HIV-1 infection (Image: Realegeno and Modlin, 2011).

2 Study Approach

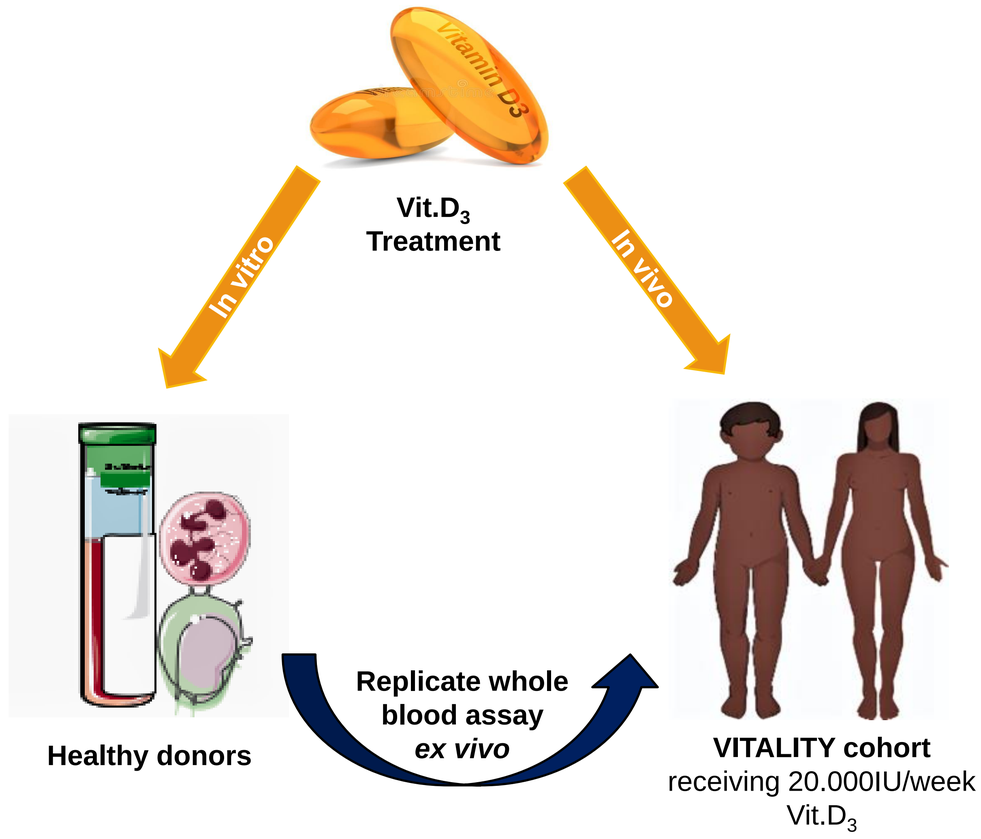


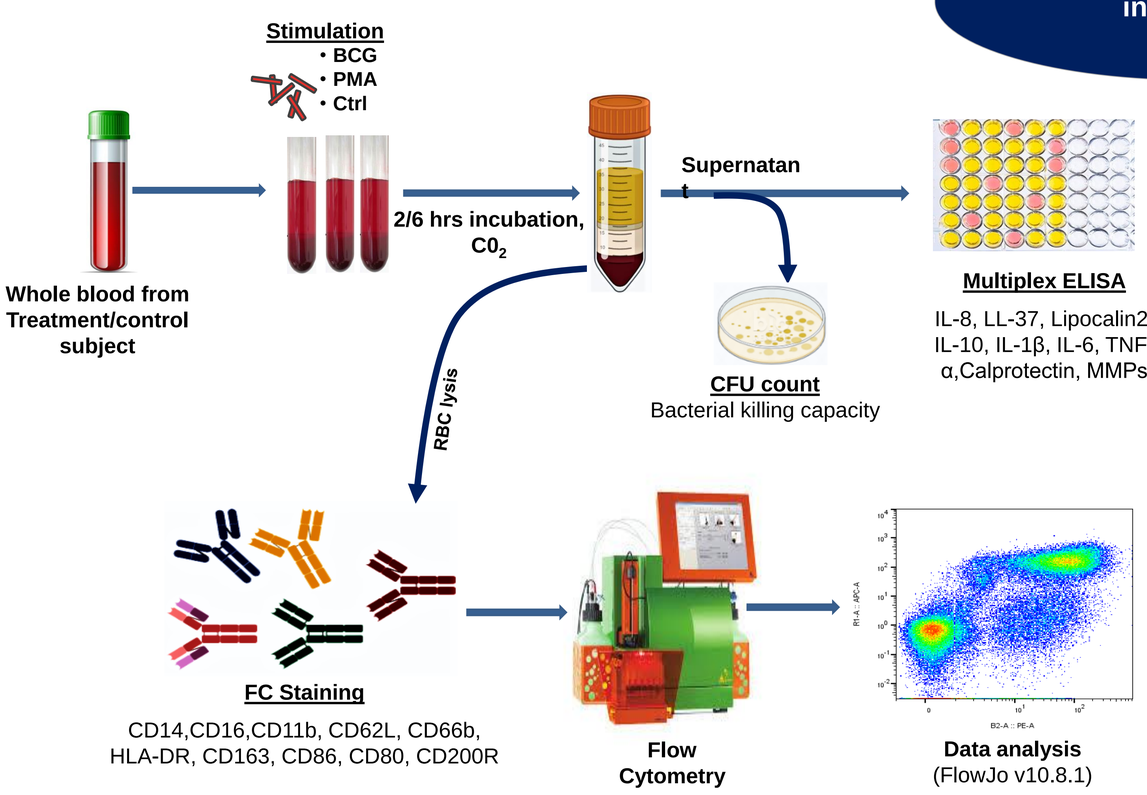
Figure 2: In vitro and In vivo vit.D3 treatment to assess impact on effector function of innate immune cells using blood collected from healthy donors and HIV-1 positive adolescents, respectively.

3 Hypothesis

Vit.D3 supplementation will enhance antimicrobial immunity, improve immune recovery and can be used as an immunomodulatory adjuvant therapy to ART in HIV-1 infected individuals

4 Methodology

a). Whole blood assay workflow



b). Macrophage study workflow

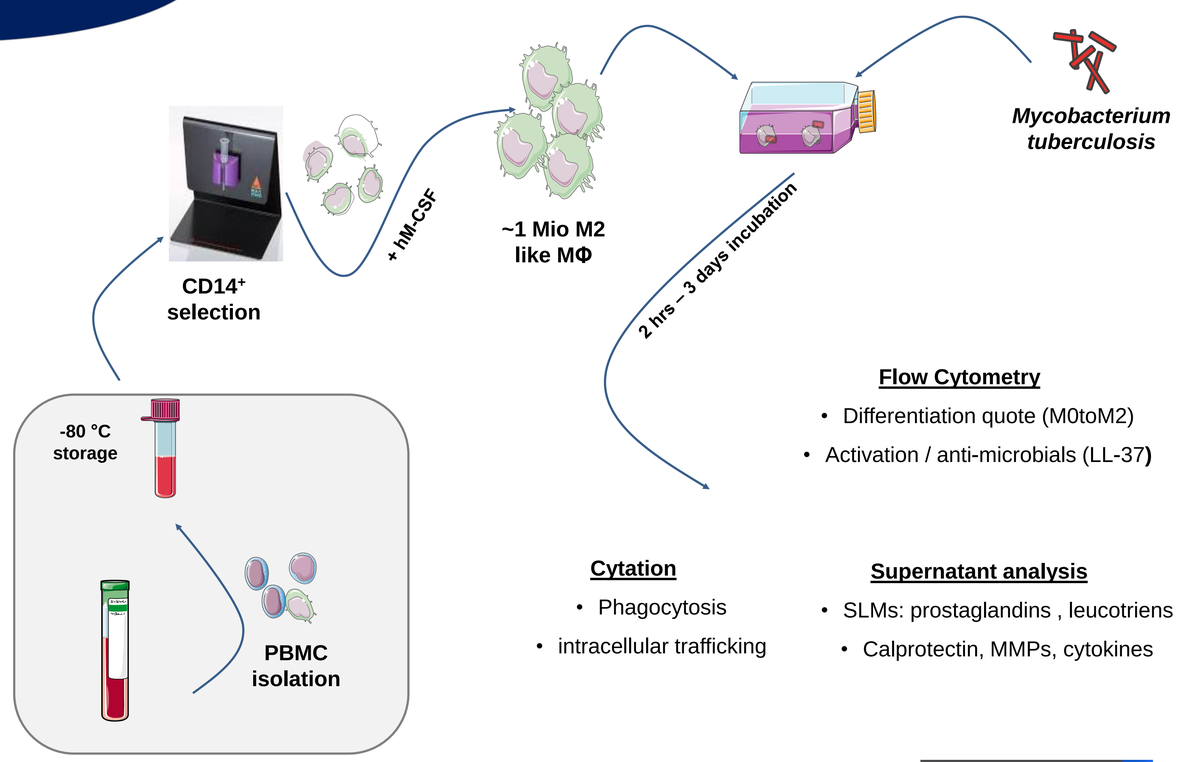


Figure 3: Whole blood assay to compare the *in vitro* and *ex vivo* effects of high dose Vit.D_3 on neutrophil activation (ROS) and monocyte polarization using flow cytometry, bacterial killing capacity (CFU count) and chemo/cytokine modulation as well as LL-37 production using multiplex ELISA **(a)**. Ex vivo differentiation of vit.D3 polarized monocytes to M1/M2 phenotype to assess macrophage phagocytosis rate, intracellular killing and necrotic cell death **(b)**.

5 Expected outcome/Outlook

- Vit.D_3 supplementation to enhance antimicrobial immunity, reduce inflammation, improve immune recovery and quality of life of HIV-1 positive adolescents
- Vit.D_3 supplementation as an immunomodulatory adjuvant therapy to ART in the HIV-1 context
- Vit.D_3 supplementation as a prophylaxis against bacterial infections in HIV-1+ individuals to promote rational use of antibiotics and reduce risk of antibiotic resistance
- Establish an improved *in vitro* model by comparing VITALITY clinical study outcome with results from *in vitro* Vit.D_3 treatment of whole blood and monocyte samples from healthy donors.

6 References

- Chun et al. (2015): https://doi.org/10.1016/j.jsbmb.2014.07.013
- Rao Muvva et al. (2020): https://doi.org/10.3389/fimmu.2019.03157
- Shawky et al. (2022): DOI: 10.21608/ejhm.2022.213785

7 Contact and Project details

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8 VITALITY Consortium