A5336:
A Randomized, Pilot Study of Ruxolitinib in Antiretroviral-Treated HIV-Infected Adults

ACTG
AIDS CLINICAL TRIALS GROUP

Background & Objectives

Objectives: (1) Evaluate the safety and tolerability of Ruxolitinib in people living with HIV who are virologically suppressed on ART; **(2)** Compare changes in IL-6 levels between participants receiving Ruxolitinib and continuing current ART

Background:

- Chronic inflammation persists for many people living with HIV despite having an undetectable viral load on ART
  - Can cause increased risk of age-related diseases and early mortality among people living with HIV
  - To date, no therapy has substantially reduced systemic inflammation for people on ART
- **Ruxolitinib:** FDA-approved Janus kinase (Jak) STAT inhibitor for myelofibrosis, polycythemia vera
  - Has shown a marked decrease in cytokines, especially IL-6
  - Potent inhibitor of HIV-1 replication AND reactivation of latent HIV-1 in primary human lymphocytes and macrophages (*in vitro*)

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Study Population

- People living with HIV between the ages of 18-74
- $CD4^+$ T cell count > 350 cells/mm^3
- On continuous ART for at least the last 2 years that contained either NNRTI or INSTI without Cobicistat, and virologically suppressed
- Had no other current or historical medical conditions (other than hypertension) or prohibited concomitant medications
- Were not pregnant

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Key Findings

- This was the first-in-class investigation of Jak 1/2 inhibitors for people living with HIV with conserved CD4+ T cells and no major comorbidities
- It demonstrated good safety and tolerability (10 mg, 2x a day, 5 weeks), provided initial insights into potential anti-inflammatory effects of this drug class
  - Significant reductions in IL-6 levels were not observed
  - Ruxolitinib decreased a number of biomarkers that are associated with poor outcomes for people living with HIV, including T cell activation, immune dysregulation, inflammation, cellular lifespan, and intestinal translocation/inflammation/ homing

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Importance & Next Steps

- Ruxolitinib is a promising anti-inflammatory agent that appears to affect many pathways associated with the development of comorbidities and death after only 5 weeks of treatment in healthy, virologically suppressed people living with HIV
- This pilot study provides a rationale for future larger studies to identify ideal populations, dose, and duration for Jak inhibitors to fully reduce systemic inflammation, HIV persistence, and clinical outcomes for virologically suppressed people living with HIV on ART
  - Ultimately, these studies can inform strategies to mitigate age-related diseases such as neurocognitive disorder, cardiovascular disease, and frailty while providing insight into a functional HIV cure

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