Characterization of the HIV-1 Transcription Profile after Romidepsin Therapy in vivo

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Introduction
Antiretroviral therapy (ART) cannot eliminate the HIV genomes integrated in latently infected cells, which are a major barrier to cure HIV (1-3).

One strategy to eradicate HIV consists of reactivating viral transcription with latency reversing agents (LRAs), such as histone deacetylase inhibitors (HDACi). A recent clinical trial, REDUC part B, analyzed the administration of the therapeutic HIV vaccine Vax-45 and rHuGM-CSF as local adjuvants in combination with the HDACi romidepsin. This approach showed an increase in unspliced cell-associated HIV RNA and residual plasma viremia after romidepsin infusions, along with a reduction in total HIV DNA (4). However, the mechanism by which romidepsin reverses HIV latency in vivo remains unclear.

Aims: To characterize the HIV transcription profile before and after romidepsin therapy in available samples from the REDUC part B study.

Methods

Study design and samples

Samples were available from only 9 of 17 trial participants, of whom only 1 had an increase in viral load in plasma after romidepsin infusions.

The parent study had sequential study interventions (vaccination and then romidepsin), and we did not have access to samples between these interventions.

5. Yukl S et al. HIV latency in isolated patient CD4+T cells may be due to blocks in HIV transcriptional elongation, completion, and splicing.

Conclusions

1. After romidepsin infusions, we observed:
- A reduction of transcriptionally silent proviruses (Fig. 6).
- An increase in HIV transcriptional initiation and especially elongation, but not completion or multiple splicing (Fig. 3-4).
- A strong correlation between time to rebound after AT1 and levels of both total HIV DNA and elongated HIV RNA (Fig. 5).

2. Romidepsin may play a role in strategies to reverse latency, but new approaches are needed to increase HIV transcriptional completion and multiple splicing, which are likely necessary for productive infection and immune recognition/killing of HIV-infected cells.

3. Therapies that increase HIV transcription but do not lead to killing of infected cells may actually shorten time to rebound after AT1.

Limitations

1. The parent study had sequential study interventions (vaccination and then romidepsin), and we did not have access to samples between these interventions and romidepsin.

2. Samples were available from only 9 of 17 trial participants, of whom only 1 had an increase in viral load after romidepsin therapy.

3. The presence of nonviral sCD45 may have affected HIV splicing and detection frequencies.

References


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Results

Romidepsin increases read-through, total, elongated, and polyadenylated but not multiply-spliced transcripts

HIV DNA and elongated transcripts predict time to viral rebound

Conclusions

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