BREACH
BELGIAN RESEARCH AIDS&HIV CONSORTIUM

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Nuclear retention of unspliced HIV-1 RNA as a reversible post-transcriptional block in latency

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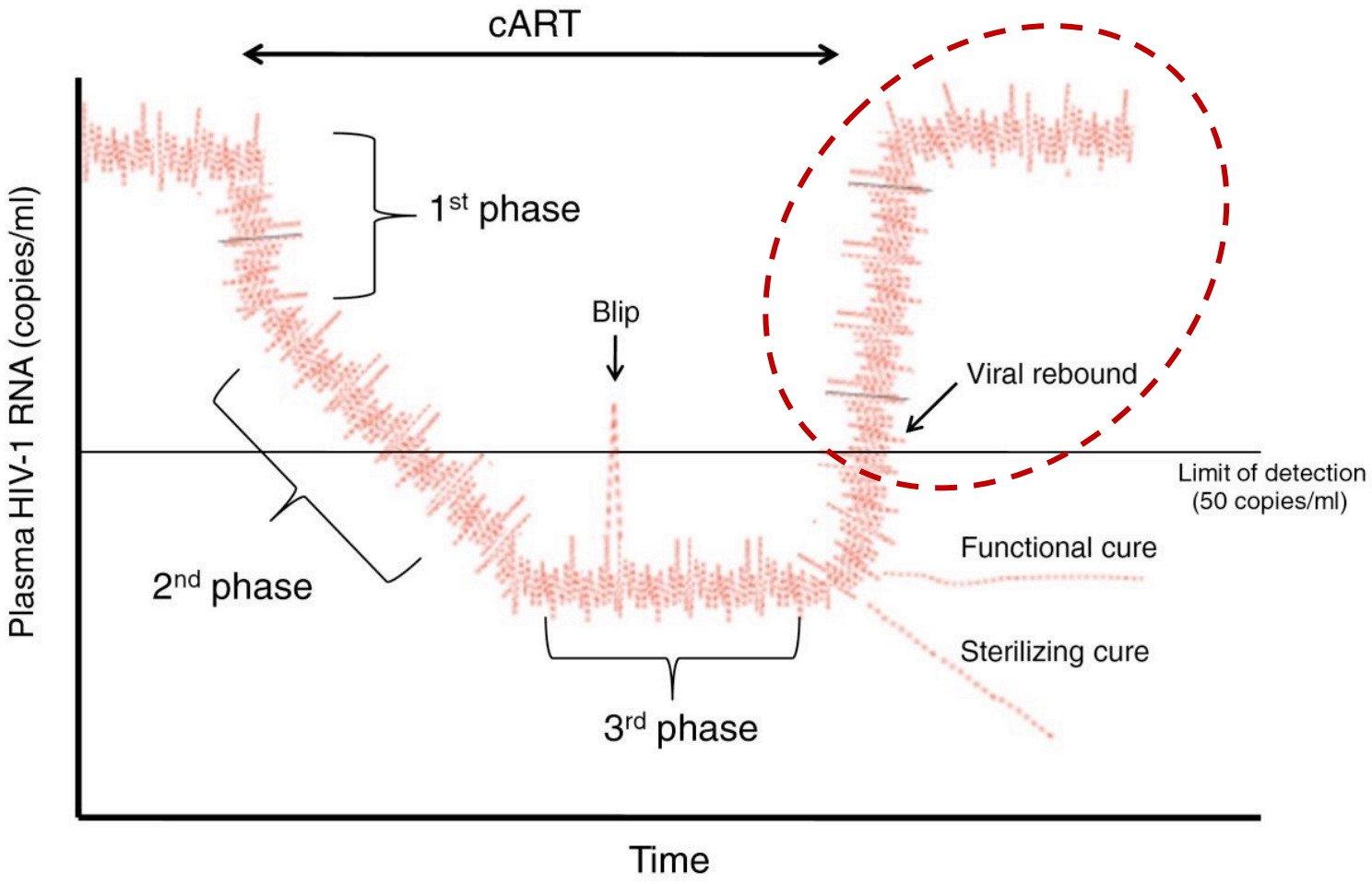
MARYAM BENDOUMOU

LABORATORY OF MOLECULAR VIROLOGY (ULB)

HEAD : PR. CARINE VAN LINT

ULB Service of Molecular Virology

Antiretroviral therapy (ART) is potent and life-prolonging but does not eradicate HIV infection



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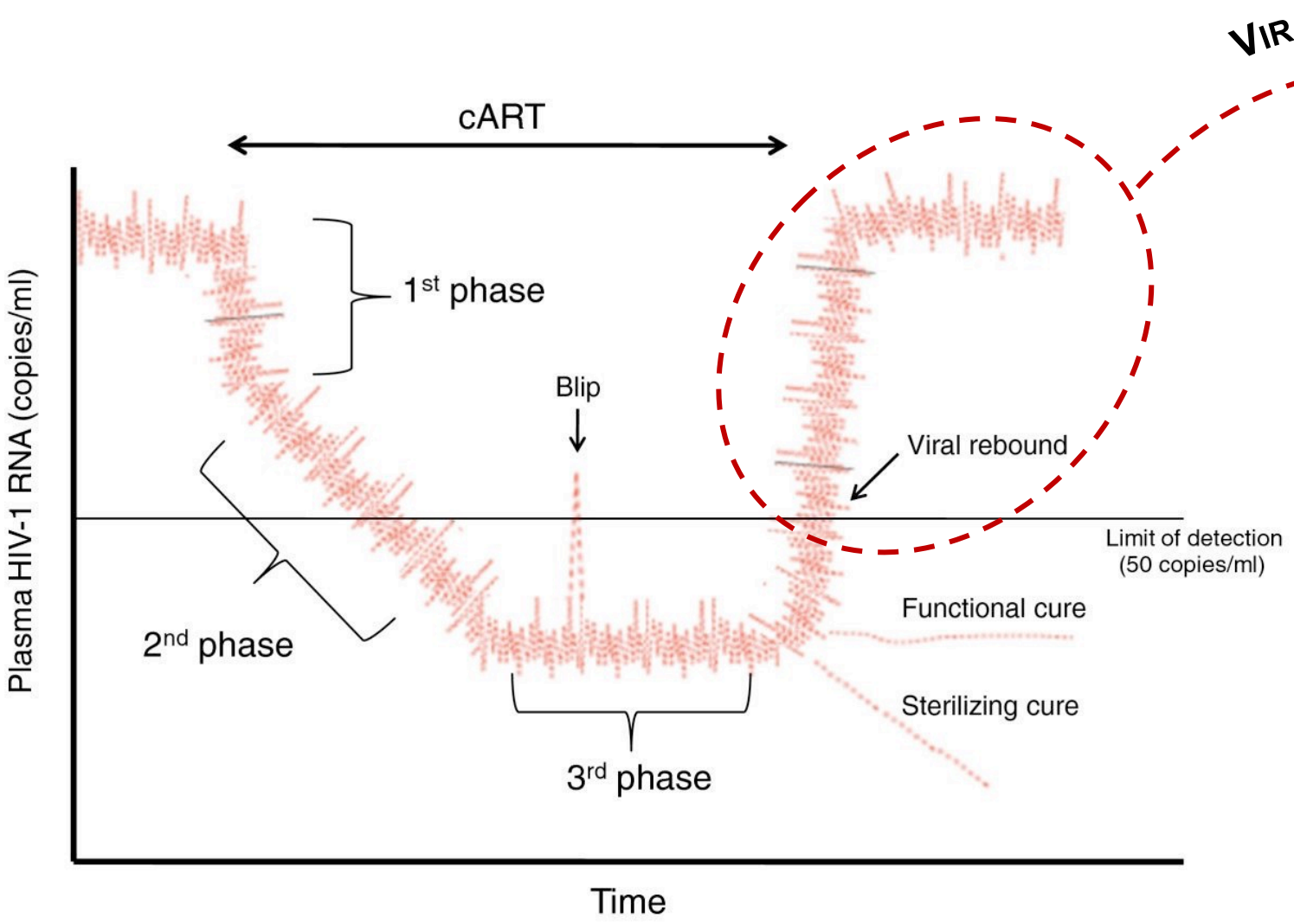

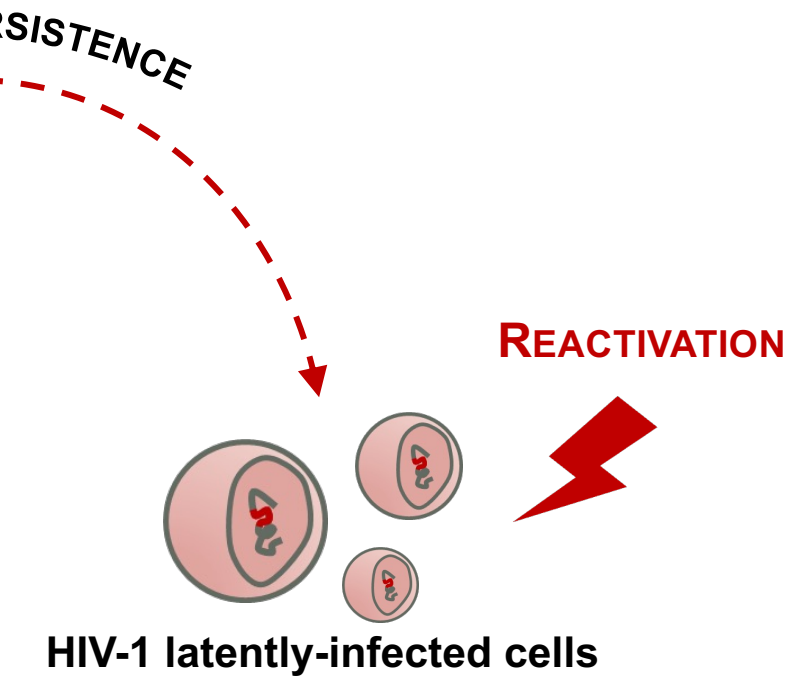

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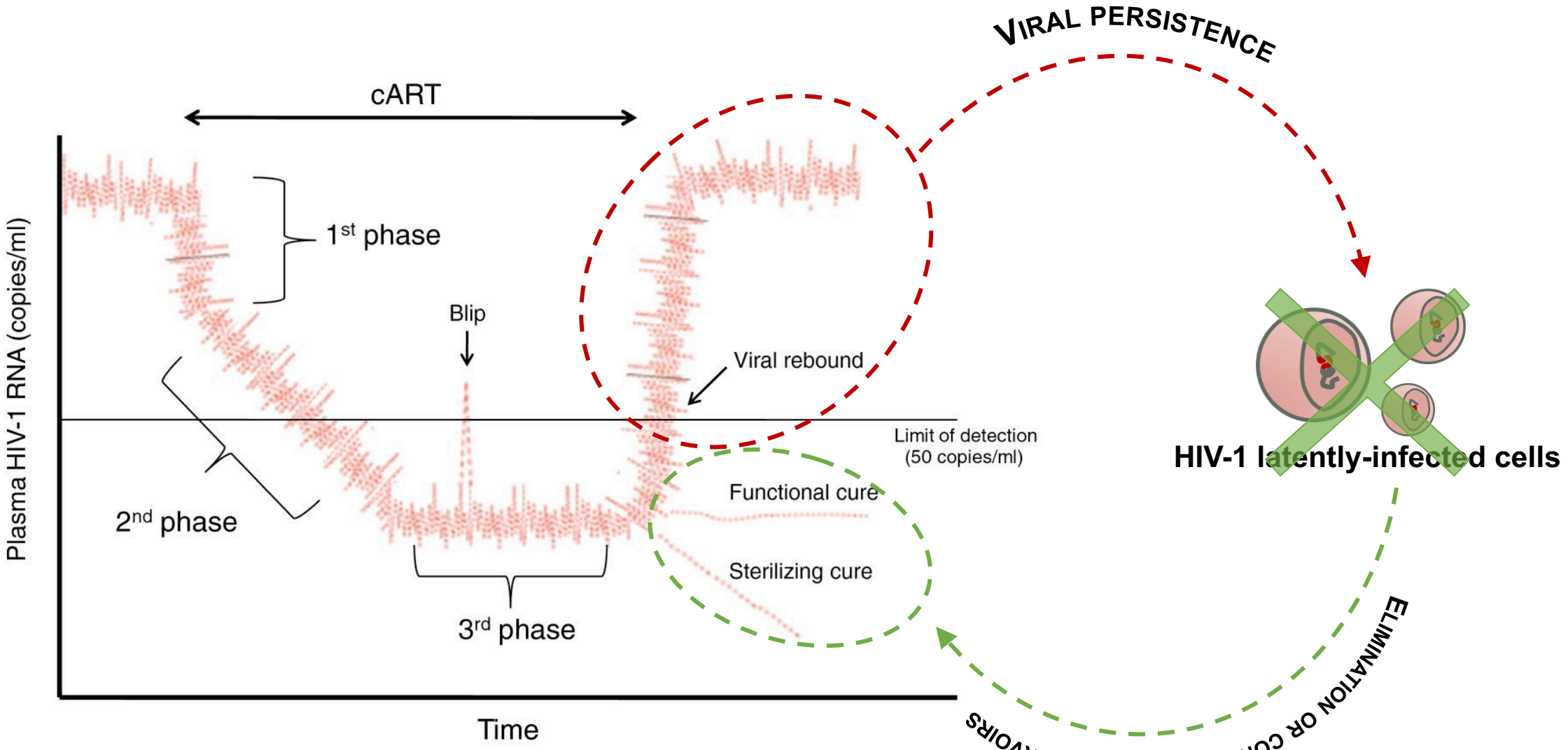
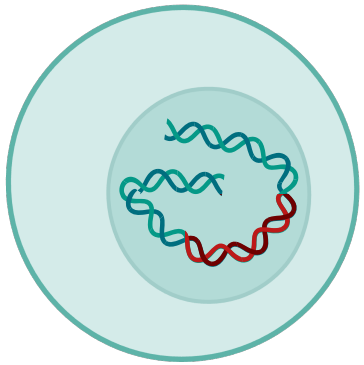
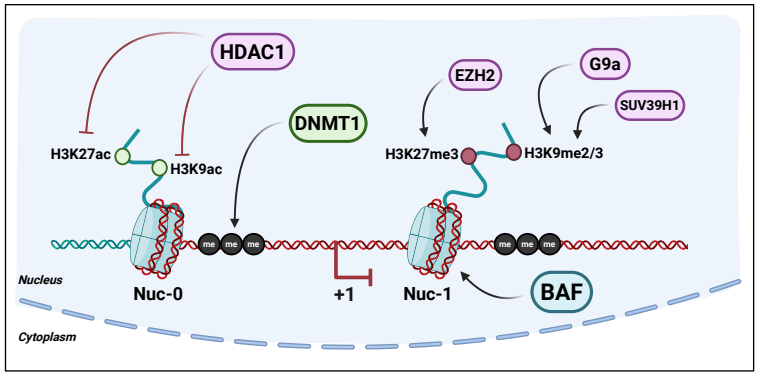


HIV-1 latency is a complex and multifactorial phenomenon

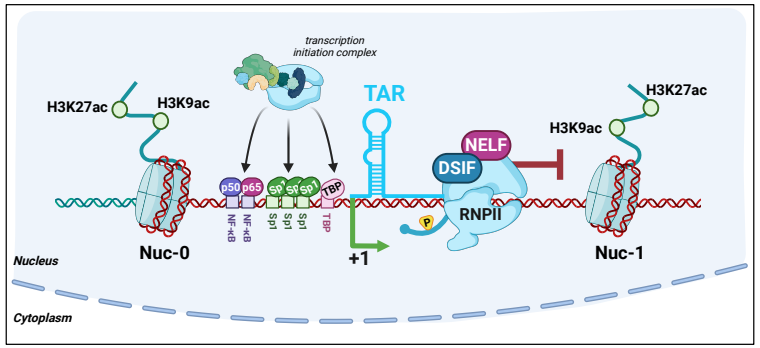


HIV-1 latently infected CD4+ T cell

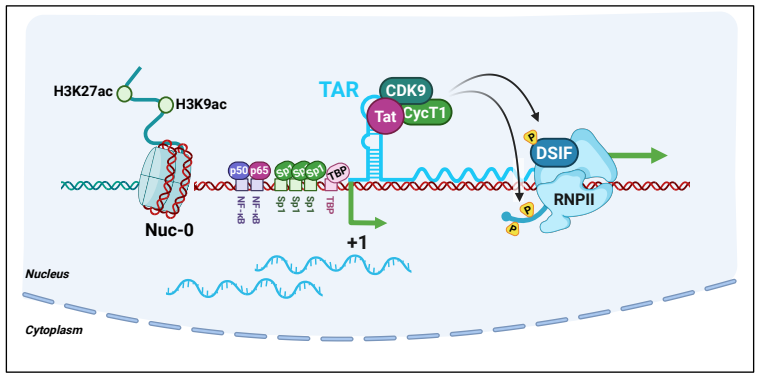
1. Epigenetically silent provirus



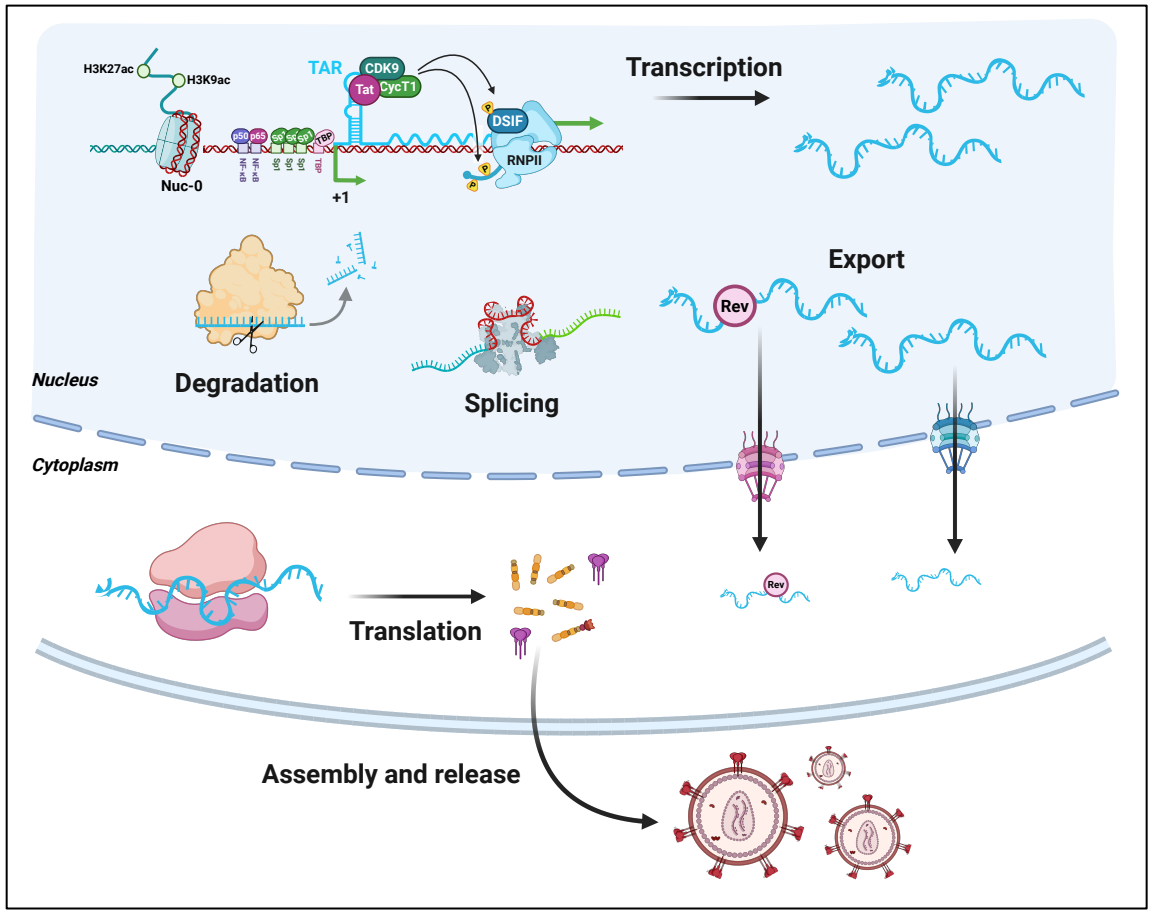
2. Transcriptional initiation



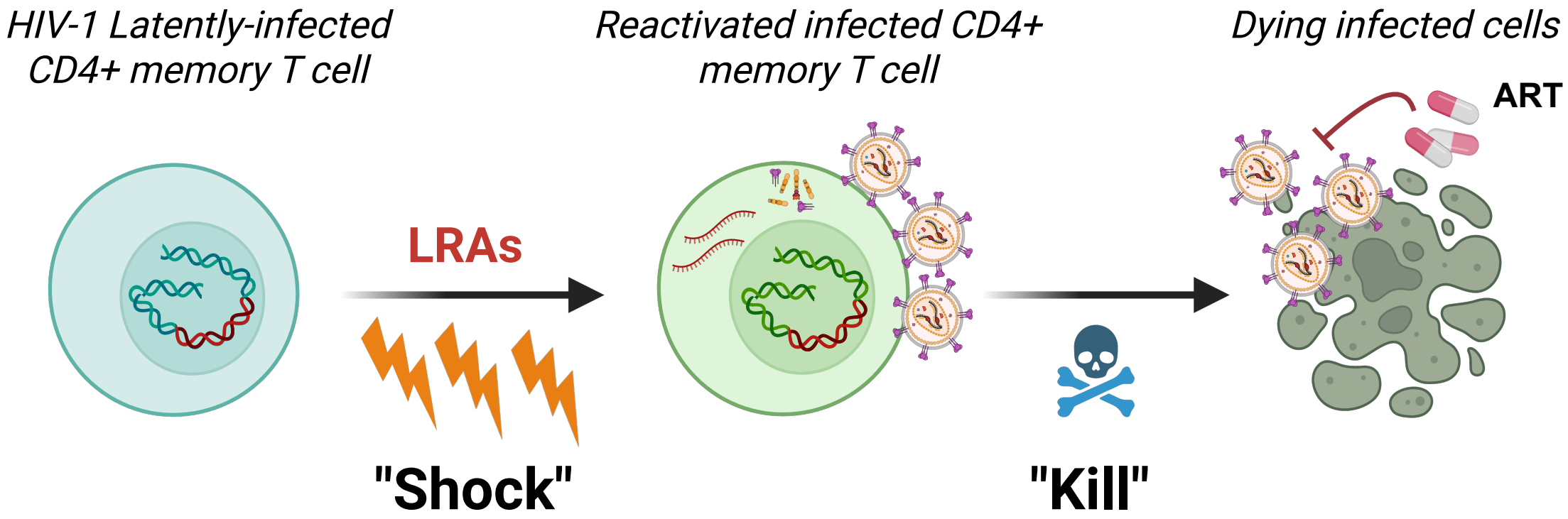
3. Transcriptional elongation



4. Post-transcriptional regulation

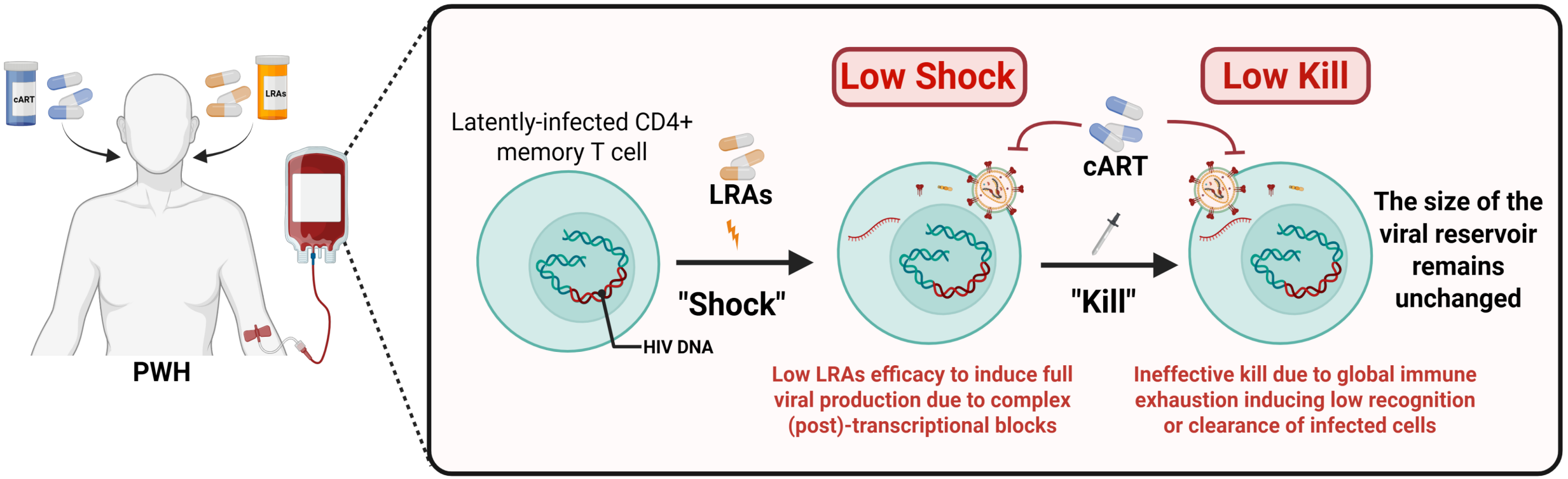


The « shock and kill » strategy for purging latent viral reservoirs is one of the most explored approaches in reaching a cure for HIV



The “shock and kill” strategy involves reactivating latent HIV-1 proviruses using latency reversing agents (LRAs), aiming at inducing viral protein expression, and exposing latently-infected cells for immune clearance

The *in vivo* clinical efficacy of current LRAs has been limited so far



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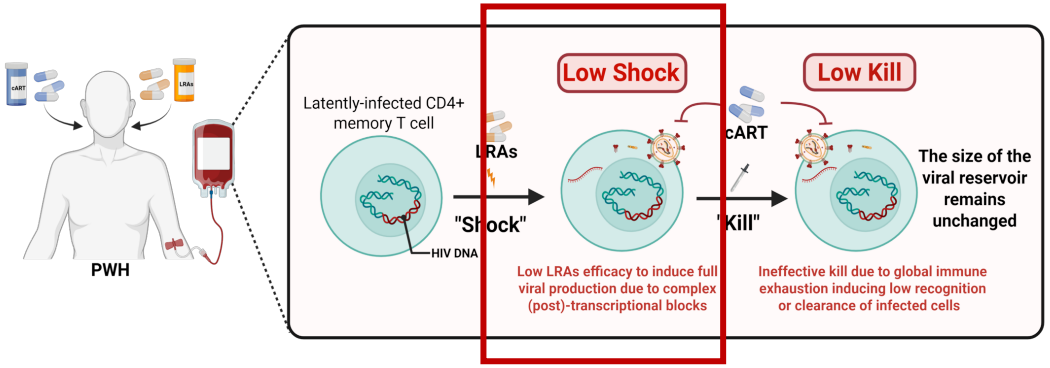

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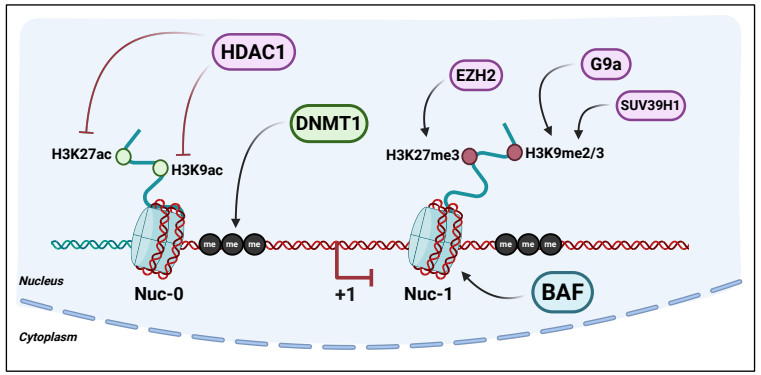

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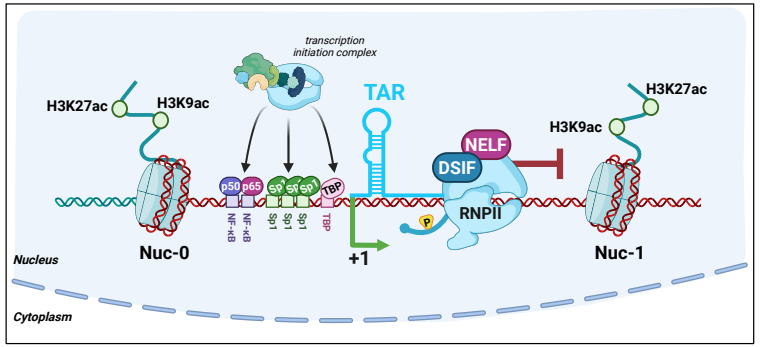

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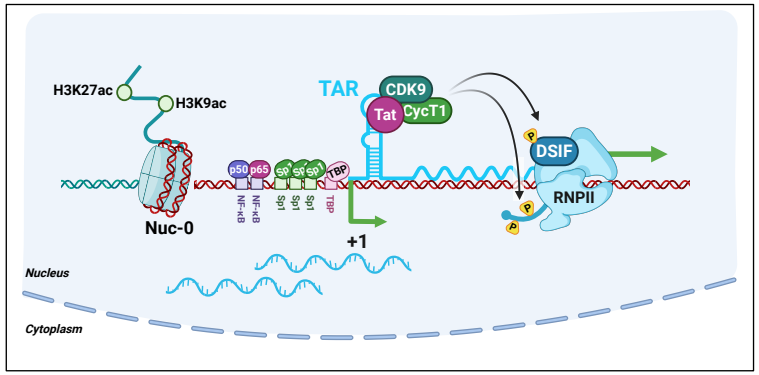
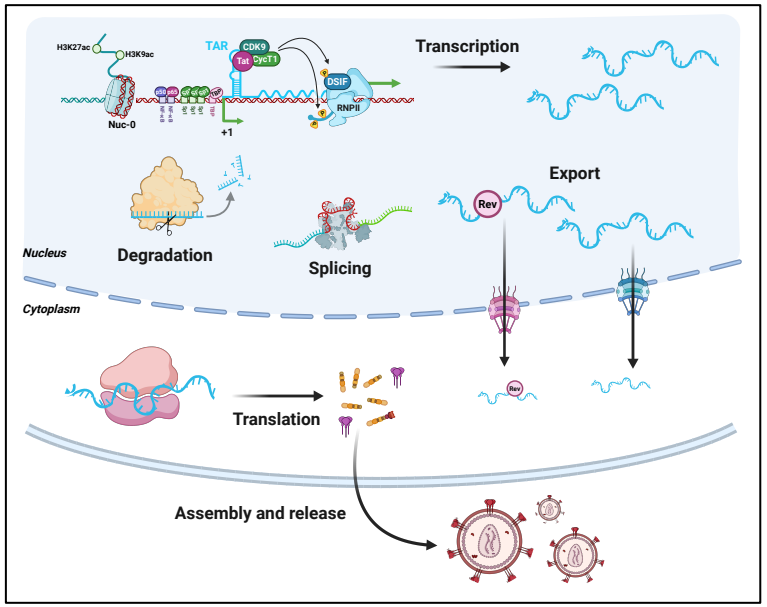


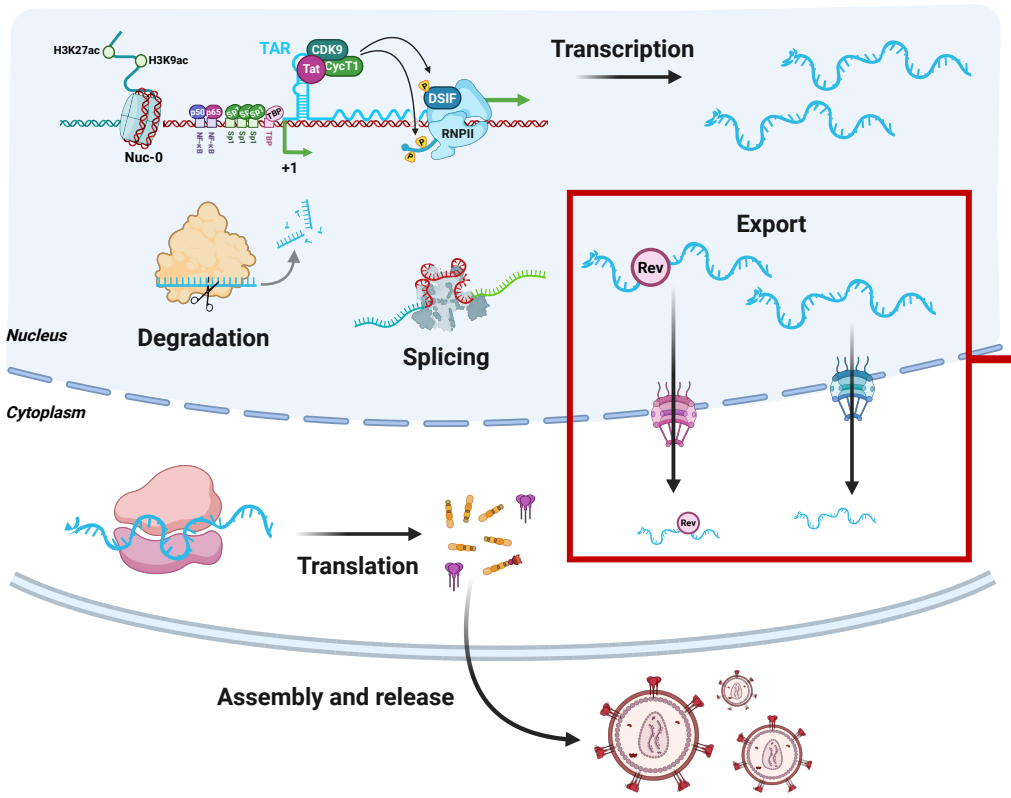
4. Post-transcriptional regulation

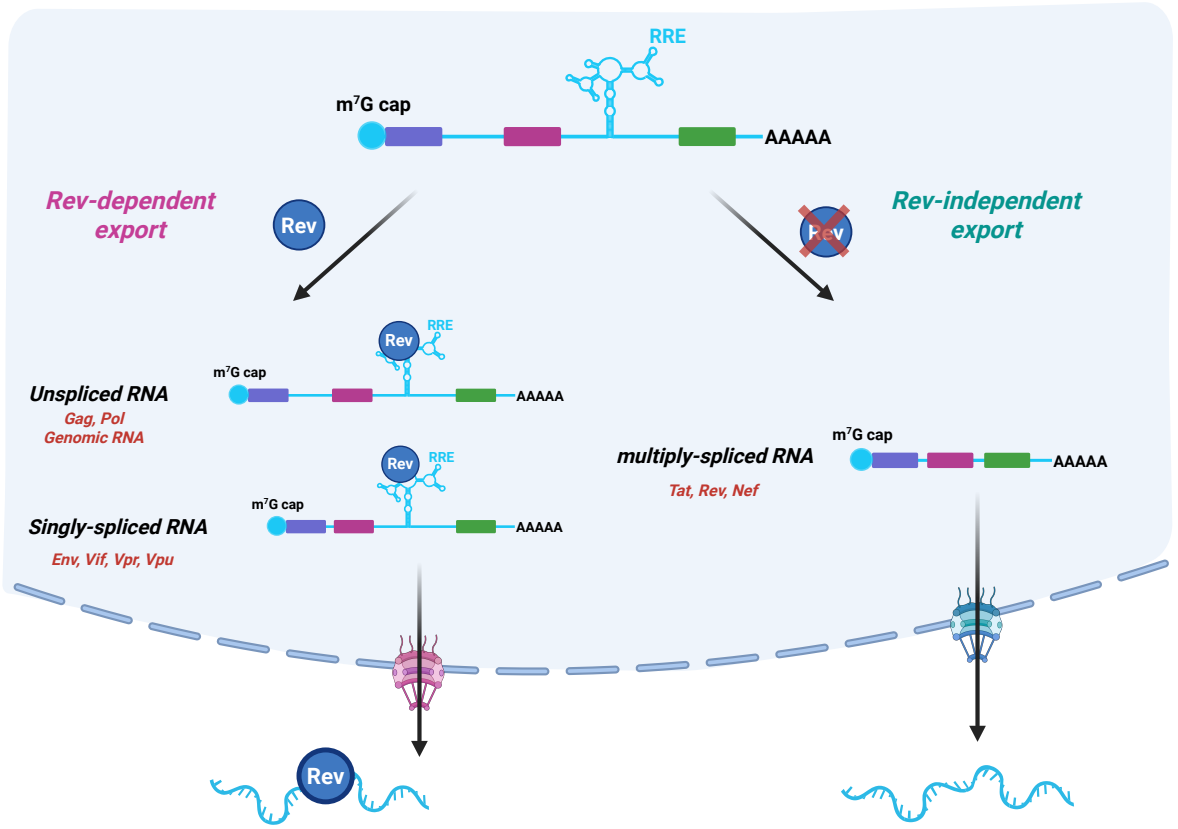


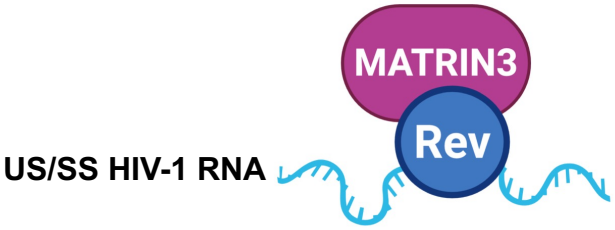
(Bendoumou and Van Lint, Current Opinion in HIV and AIDS 2025)

The neglected role of post-transcriptional blocks in HIV-1 gene regulation

4. Post-transcriptional regulation



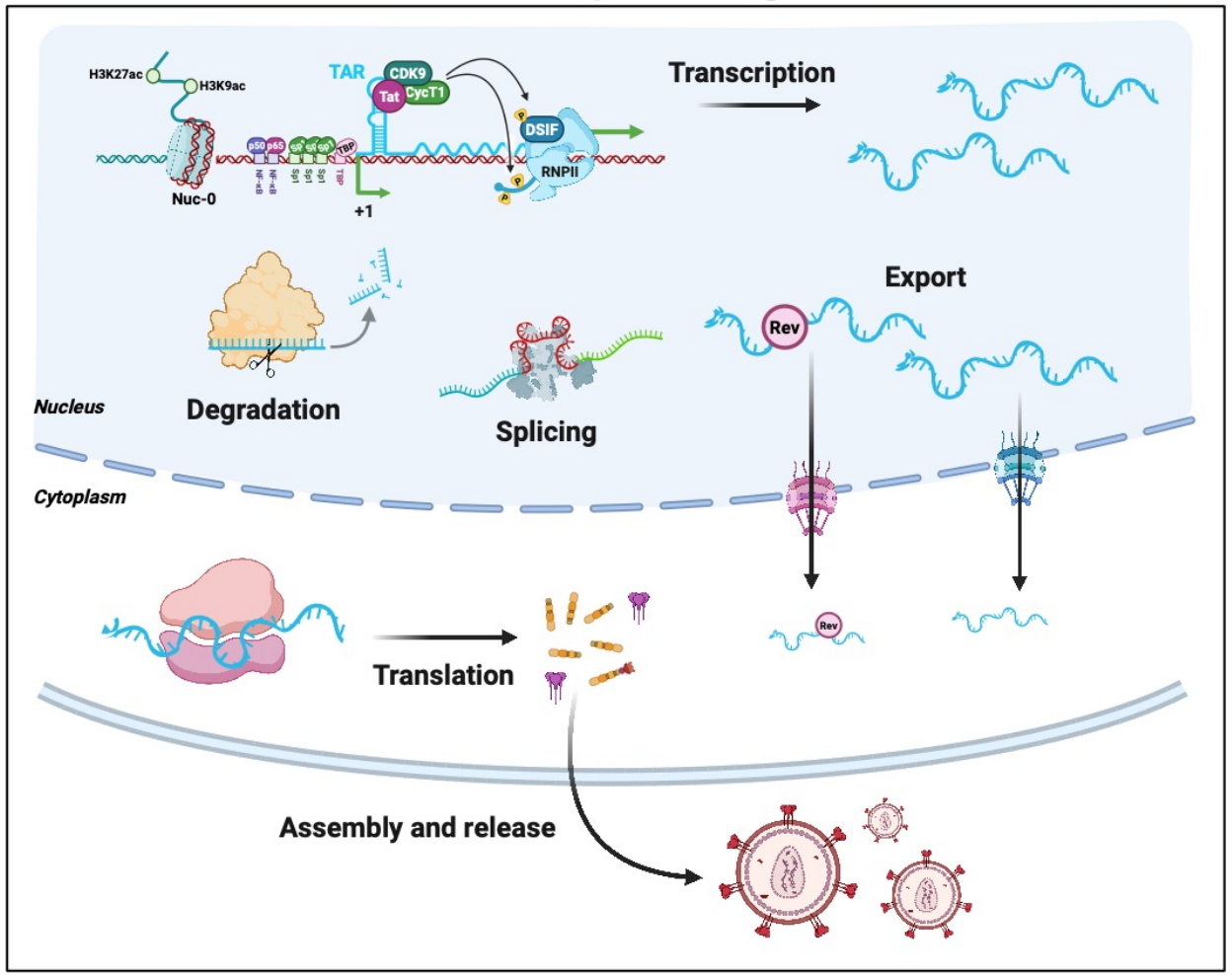




→ **Rev-MATRIN3 complex is essential for the export of HIV-1 US/SS RNA.**

(Sarracino *et al.*, mBio 2018).

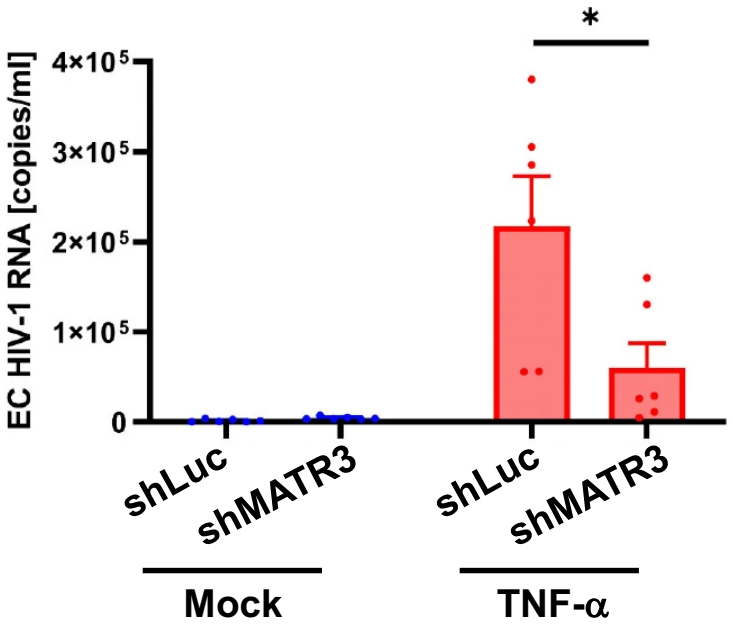
Objectives of the publication



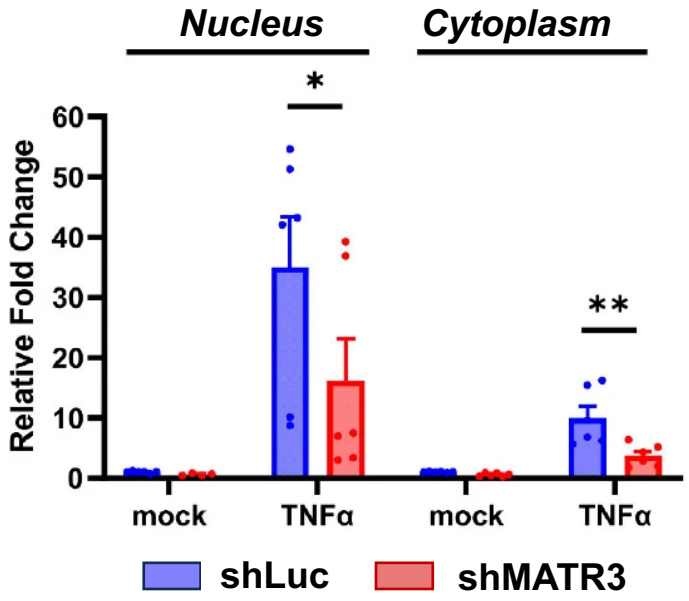
As Rev is essential for productive infection and viral rebound, understanding the molecular regulation of Rev-dependent RNA processing is critical for advancing “shock-and-kill” and other HIV cure strategies.

Rev co-factor MATR3 stabilizes HIV-1 RNA during reactivation

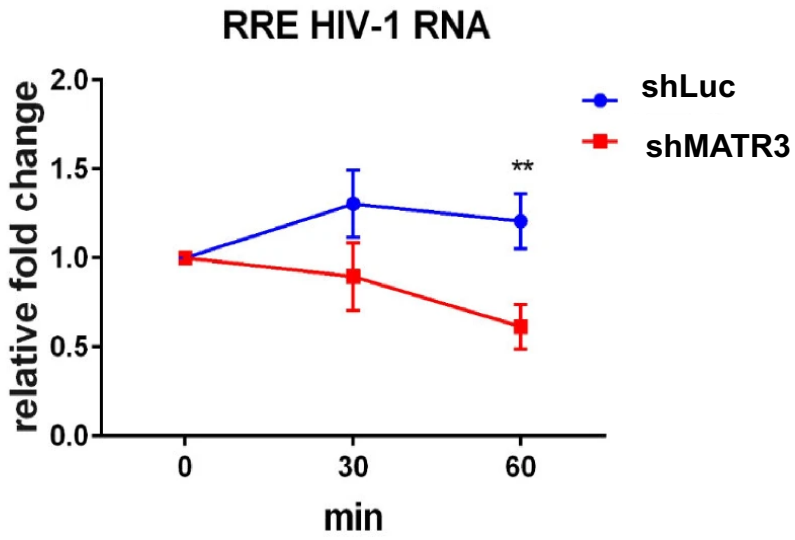
Viral particle release



Rev-dependent export



Stability of Rev-dependant HIV-1 RNA



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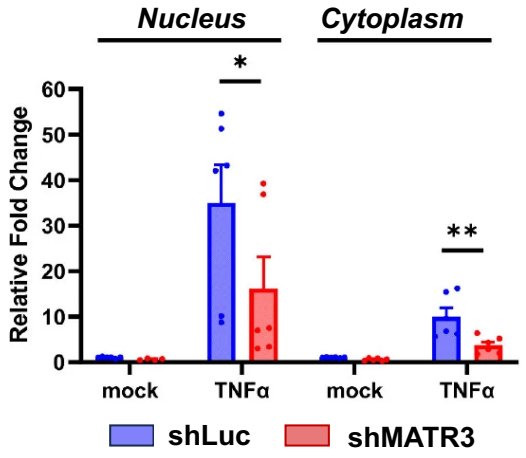
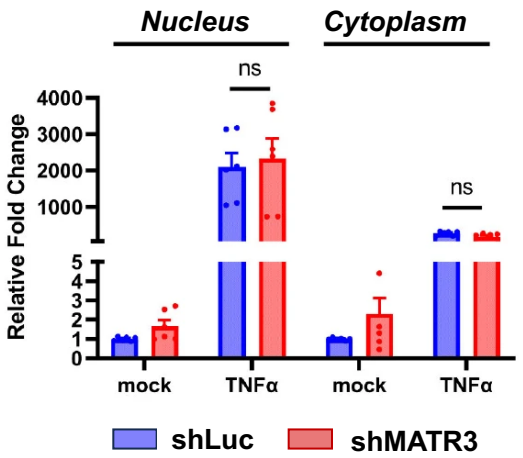
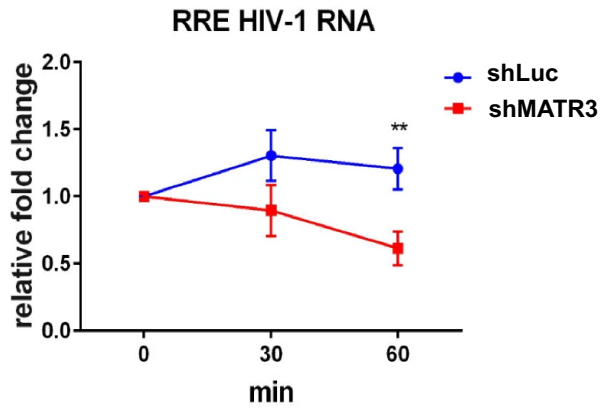
Rev-dependent export (RRE)



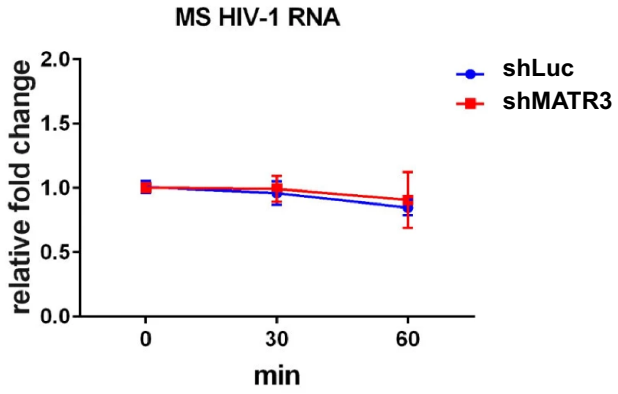
Rev-independent export (MS)



Stability of Rev-dependant HIV-1 RNA

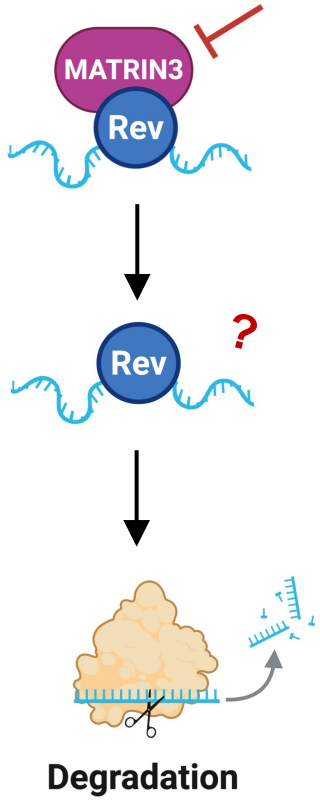


Stability of Rev-independant HIV-1 RNA



MATRIN3 depletion:

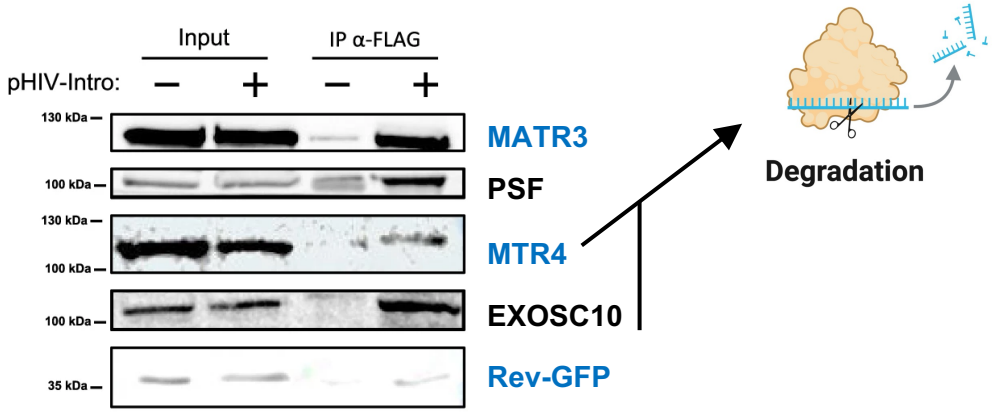
- Decreases viral particle production.
- Decreases Rev-dependant export
- **Decreases the pool of Rev-dependant HIV-1 RNA**



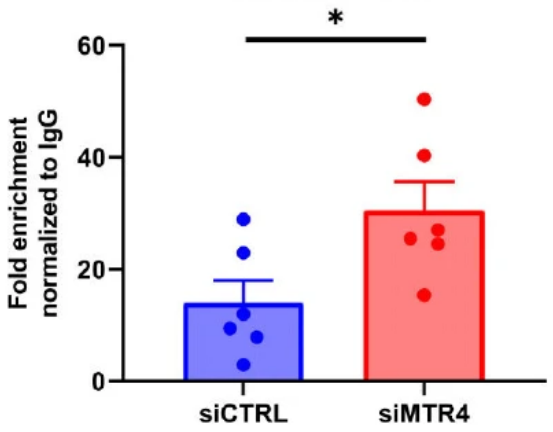
Intron-containing HIV-1 RNA (US and SS) can be degraded by the cellular RNA surveillance machinery

MATR3/MTR4/Rev ribonucleoprotein complex regulates the fate of Rev-dependent HIV-1 RNA

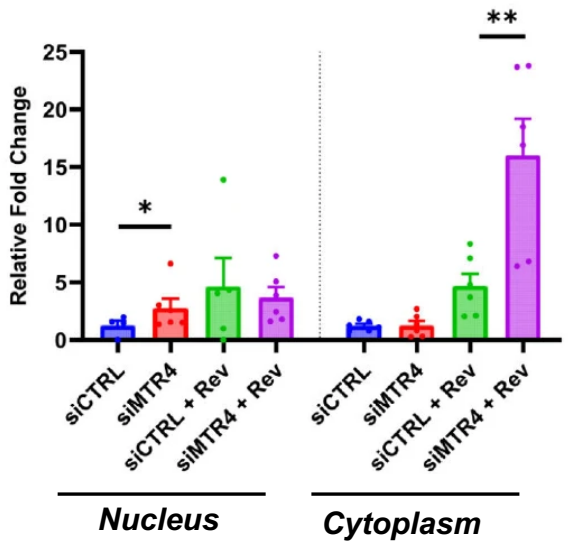
HIV-1 RNA pull down



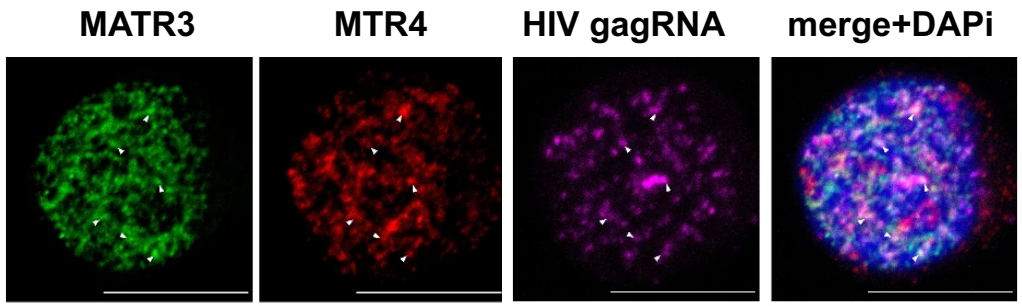
MATR3 interaction with HIV-1 RNA



Rev-dependant export



HIV gagRNA immunofish

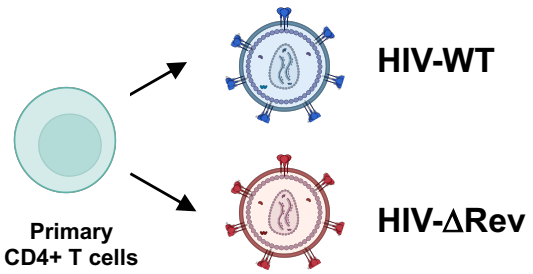


- MATR3/MTR4/Rev complex interacts with HIV-1 RNA
- MTR4 depletion increases MATR3 interaction with US HIV RNA
- **MTR4 depletion increases Rev-dependant export**

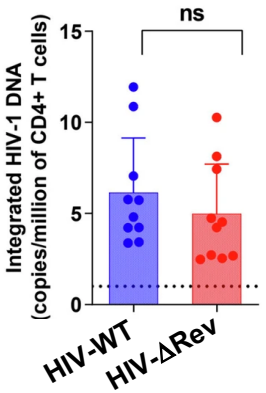
Regulation ?

MATR3 >< MTR4

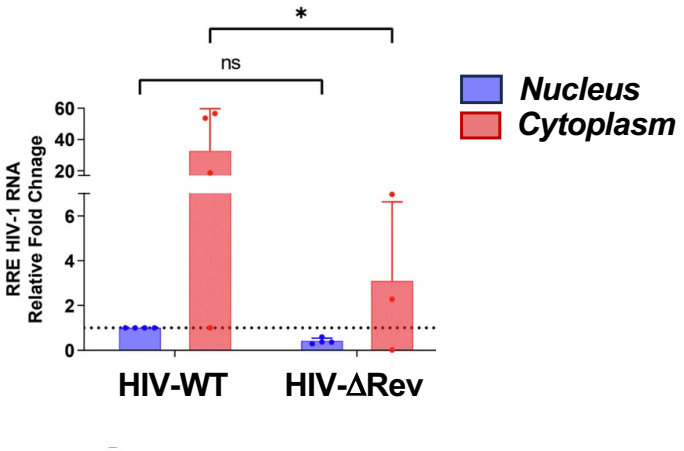
Rev determines the MATR3-MTR4 binding to HIV-1 RNA



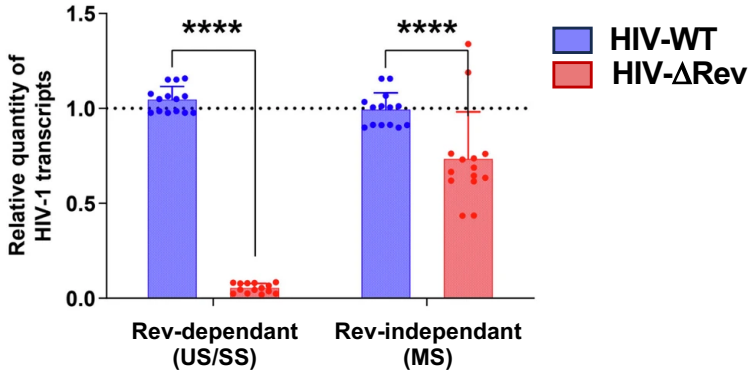
Integration



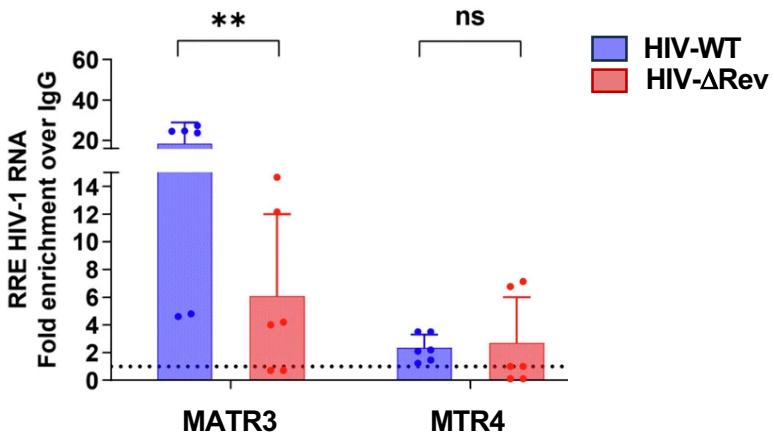
Rev-dependent export

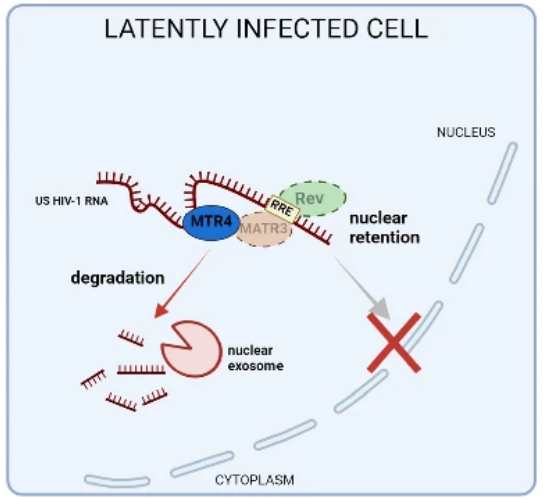


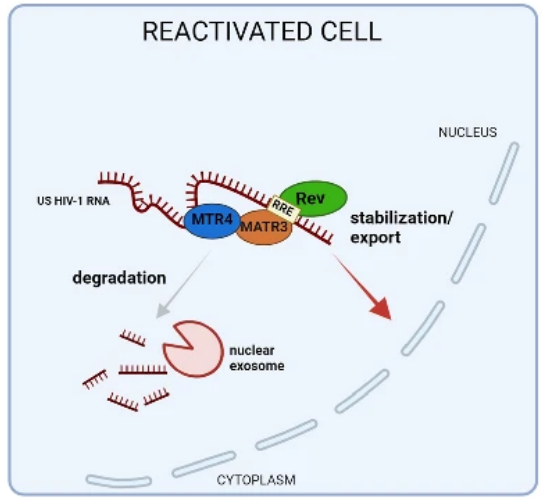
HIV-1 RNA levels



Recruitment to Rev-dependant HIV-1 RNA



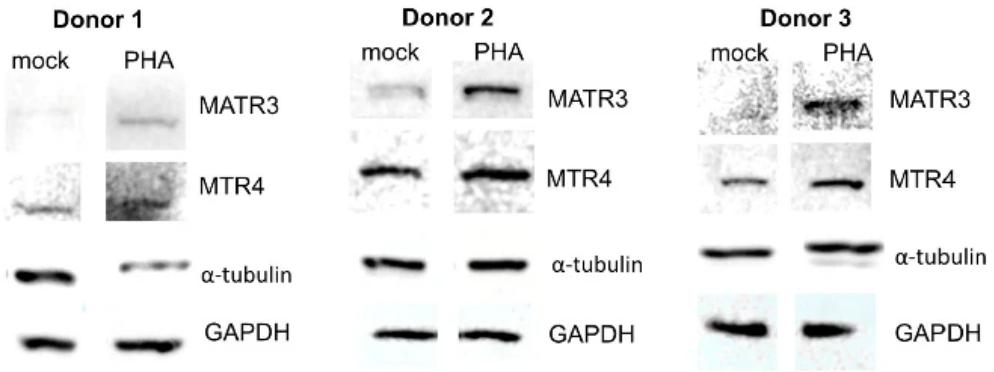




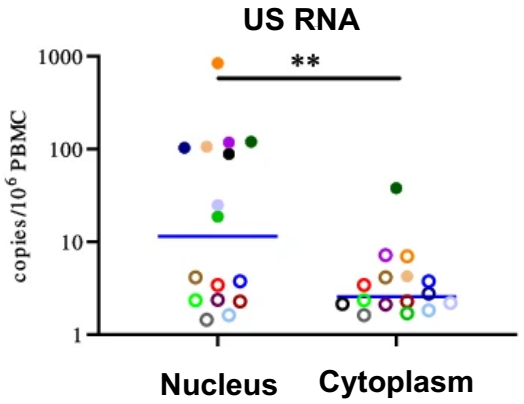
MATR3 protects Rev-dependant HIV-1 RNAs from MTR4-mediated degradation

Nuclear retention of US HIV-1 RNA in PBMCs from 22 ART-treated PWH

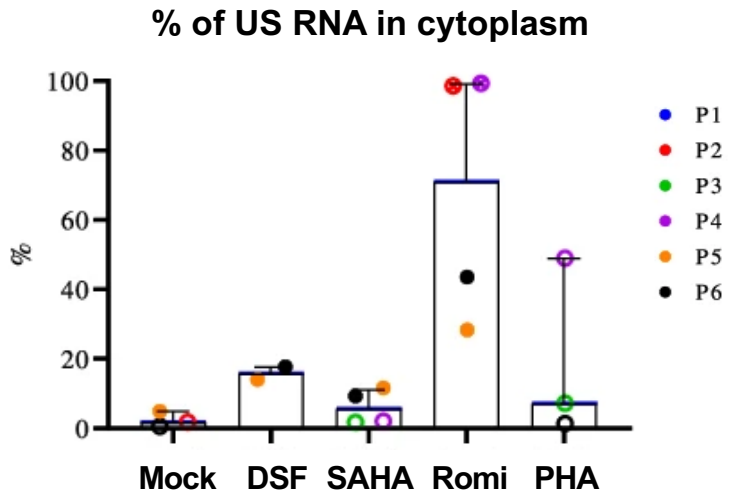
MATR3/MTR4 protein levels in PWH PBMCs



Rev-dependant export



LRA-potency to promote Rev-dependent export



- In Unstimulated PBMCs from PWH **MATR4 >>>> MATR3.**
- **In PBMCs from PWH HIV-1 US RNA is retained in the nucleus.**
- **The HDACi Romidepsin, one of the most potent LRA, promotes Rev-dependant export.**

Take home message

- ***Clinical Insight***:

  Post-transcriptional restrictions persist even after transcriptional reactivation, limiting viral protein production and explaining (in part) why current latency reversing agents (LRAs) have not so far achieved significant reductions in the HIV reservoir size.

- ***Mechanistic finding***:

  Reduced MATR3 and elevated MTR4 expression in ART-treated people with HIV may promote nuclear retention and degradation of viral RNA, contributing to long-term viral persistence.

- ***Therapeutic Implication*** :

  To fully reactivate or silence latent HIV, **cure strategies must address both transcriptional and post-transcriptional barriers**

- ***Future direction***:

  Understanding how this MATR3-MTR4 “switch” is regulated could provide new insights into the mechanisms of viral RNA stability and degradation and be critical for the design of innovative strategies to eliminate latent HIV.

Acknowledgments

Study Participants

St-Pierre Hospital, Brussels, Belgium
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