

BREACH
BELGIAN RESEARCH **AIDS&HIV** CONSORTIUM

13th Breach Symposium
Thursday 27th November 2025

From epigenetics to post-transcriptional events: How UHRF1 orchestrates multiple layers of HIV-1 gene expression

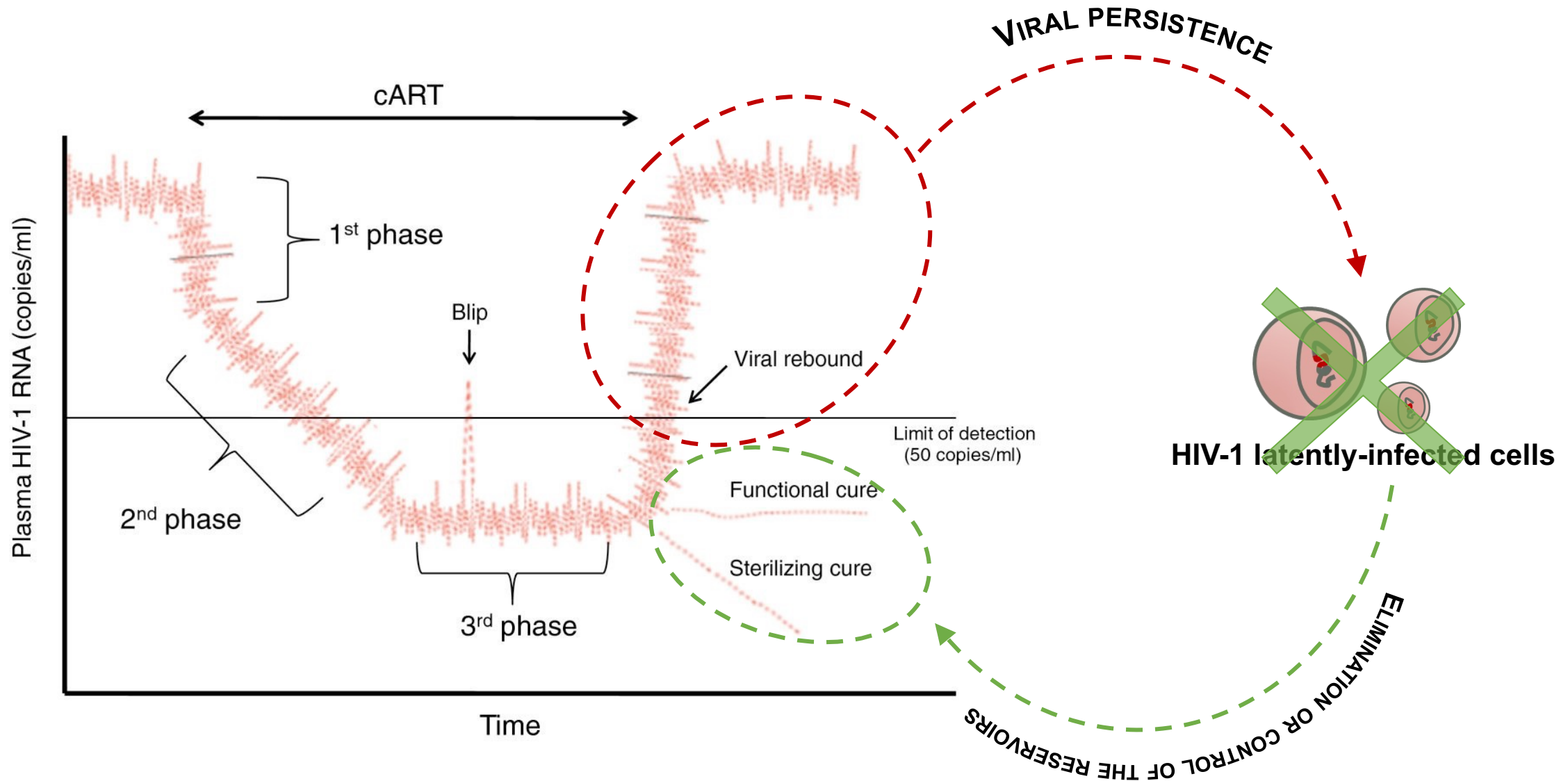
Maryam BENDOUMOU, Lisa PILOSIO, Antoine DUTILLEUL, Lorena NESTOLA, Amina AIT AMMAR1 and Carine VAN LINT.



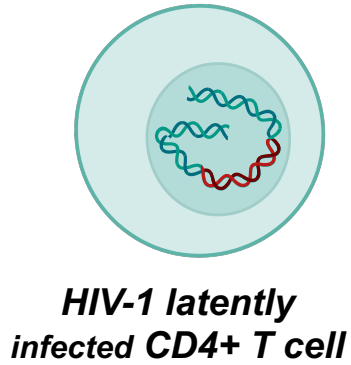
MARYAM BENDOUMOU
LABORATORY OF MOLECULAR VIROLOGY (ULB)
HEAD : PR. CARINE VAN LINT



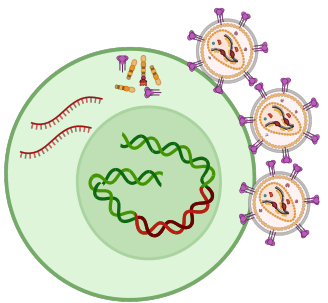
Antiretroviral therapy (ART) is potent and life-prolonging but does not eradicate HIV infection



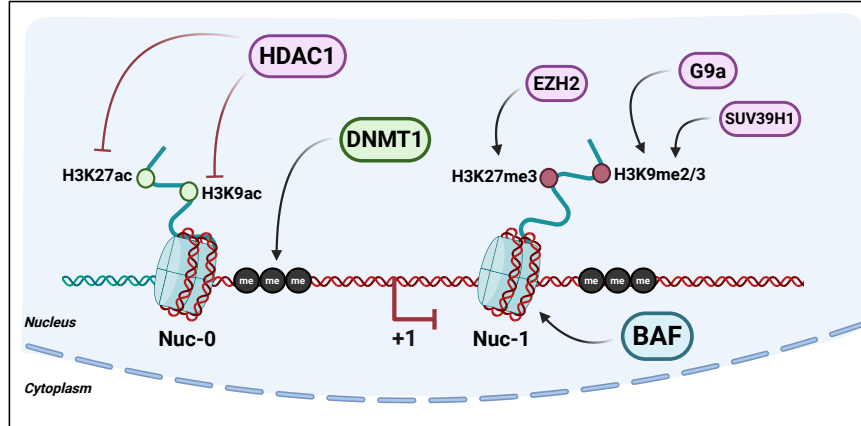
HIV-1 latency is a complex and multifactorial phenomenon



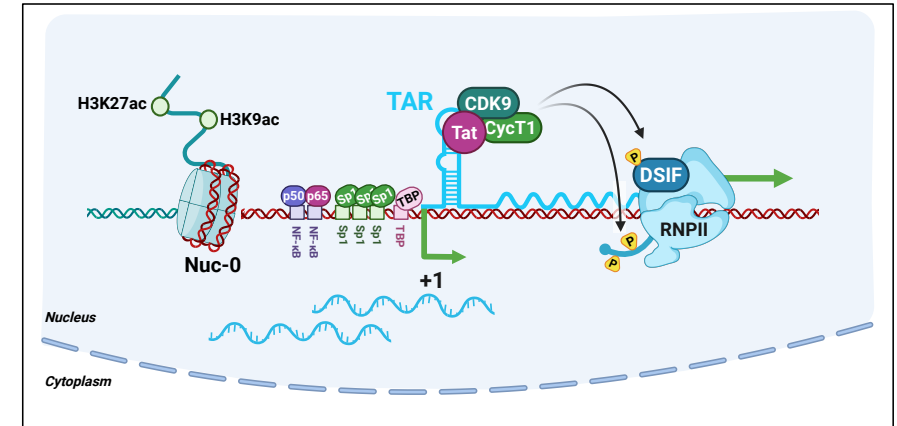
Full reactivation



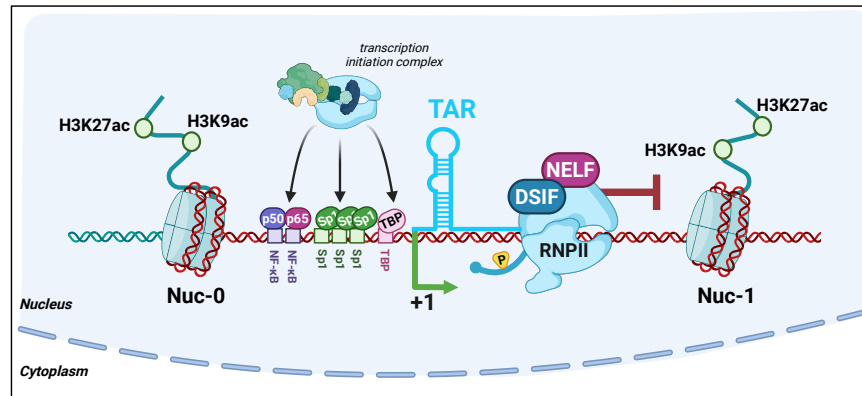
1. Epigenetically silent provirus



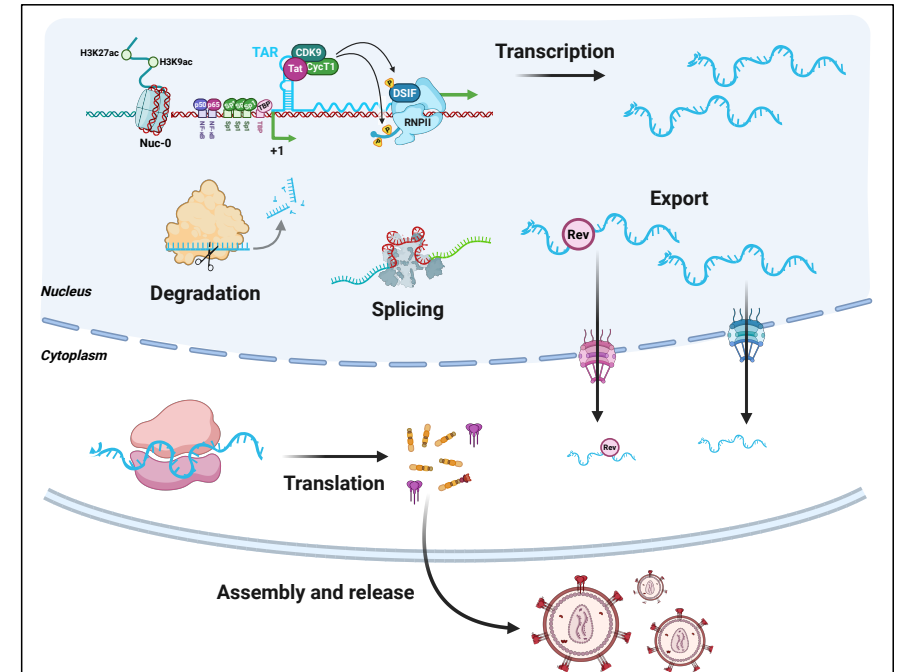
3. Transcriptional elongation



2. Transcriptional initiation

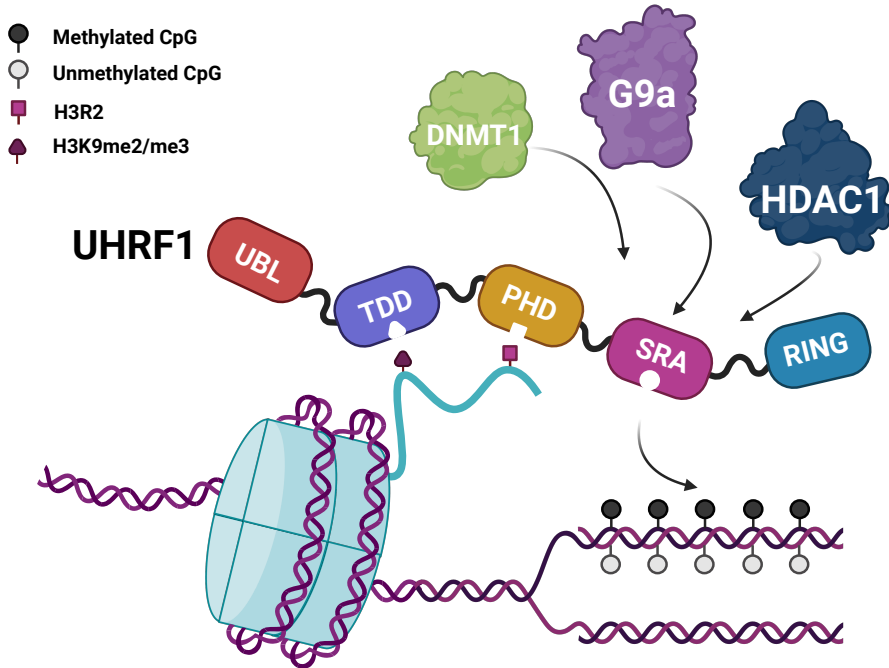


4. Post-transcriptional regulation



The epigenetic integrator UHRF1 represses HIV-1 gene expression at the epigenetic and transcription elongation levels

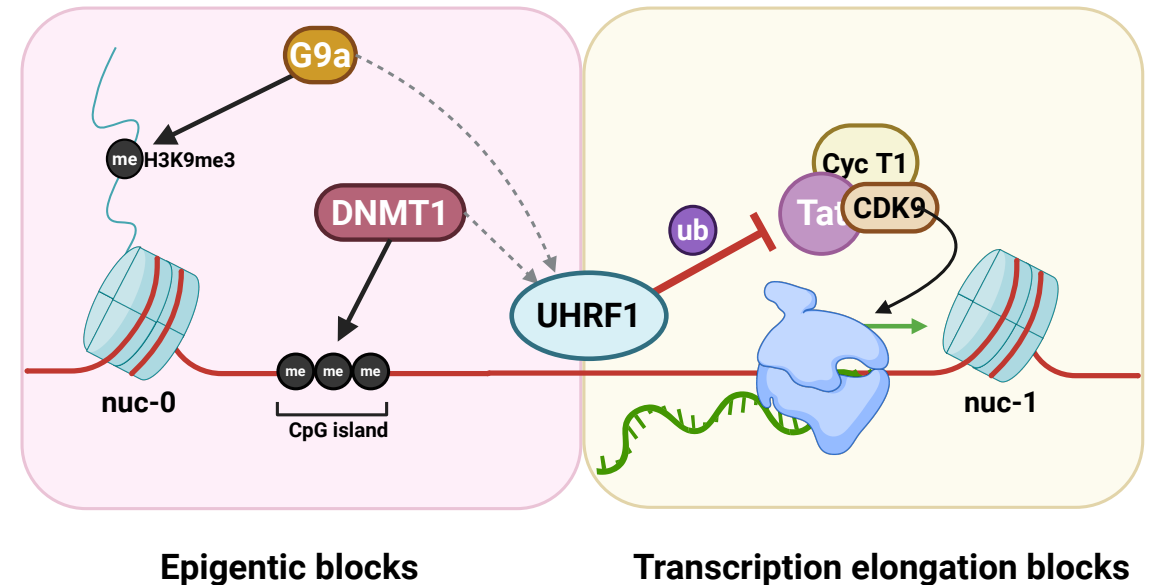
Cellular function



Function in HIV-1 gene expression regulation

(Verdikt and Bendoumou et al, Ebiomedicine 2022)

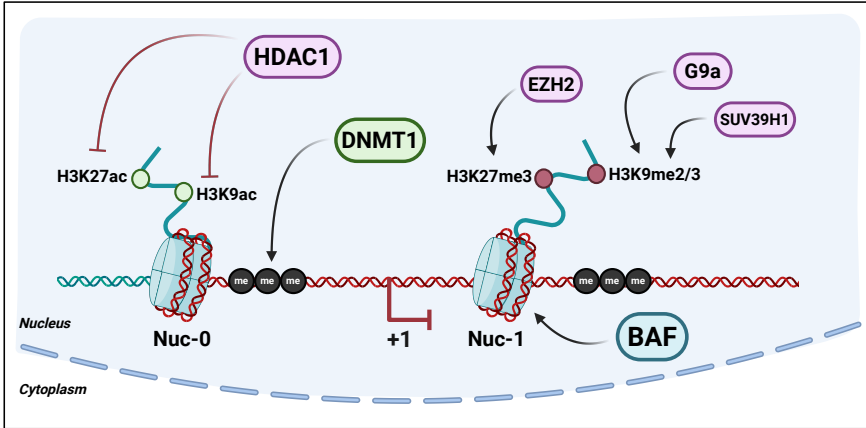
(Liang et al, Mbio 2021)



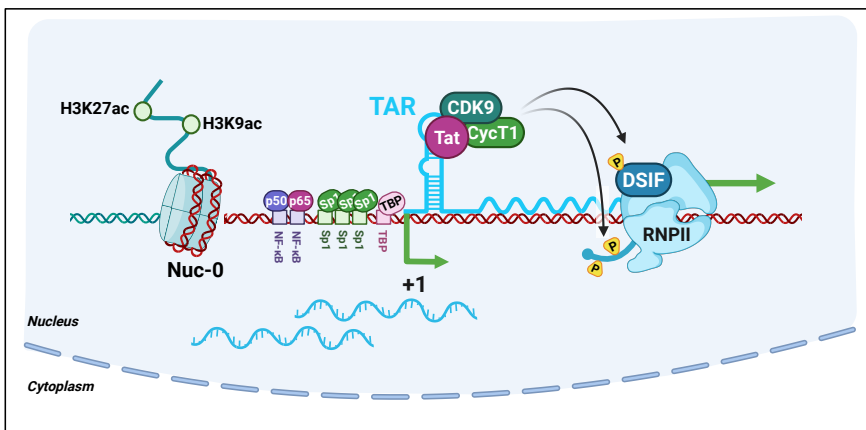
- > **UHRF1** : Ubiquitin-like with PHD and RING finger domain 1.
- > **Function**: maintain the epigenetic profiles during cellular replication.
- > **Pathologies** : - overexpressed in several cancers.
- represses HIV-1 gene expression (latency)

The epigenetic integrator UHRF1 represses HIV-1 gene expression at the epigenetic and transcription elongation levels

1. Epigenetically silent provirus



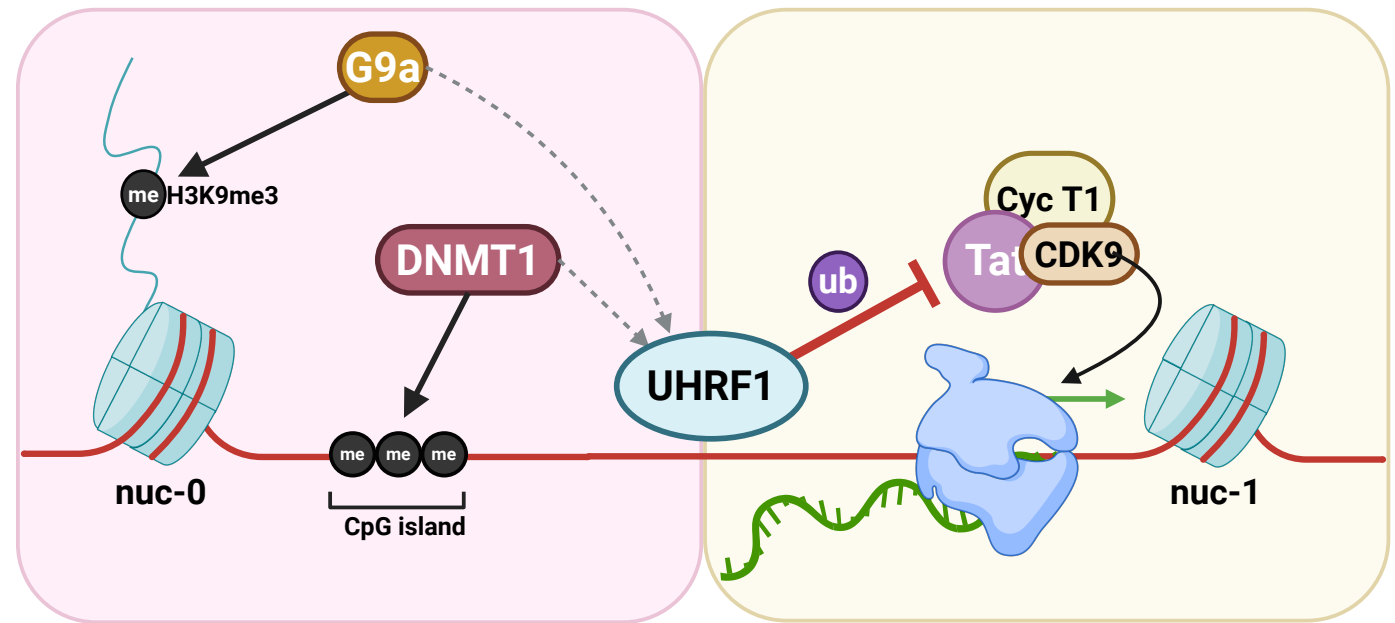
3. Transcriptional elongation



Function in HIV-1 gene expression regulation

(Verdikt and Bendoumou et al, Ebiomedicine 2022)

(Liang et al, Mbio 2021)



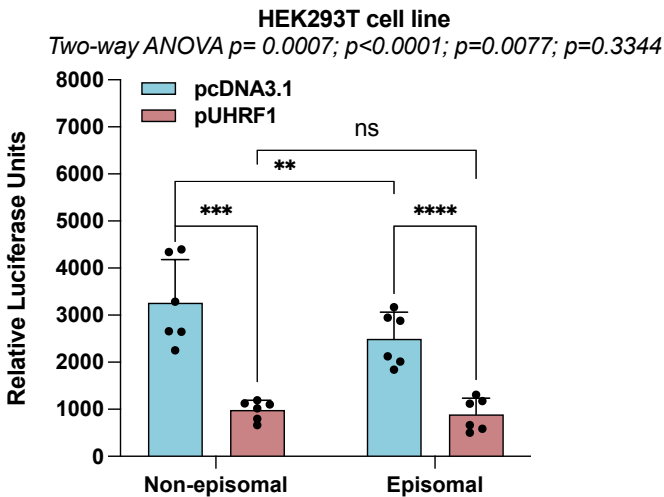
Epigenetic blocks

Transcription elongation blocks

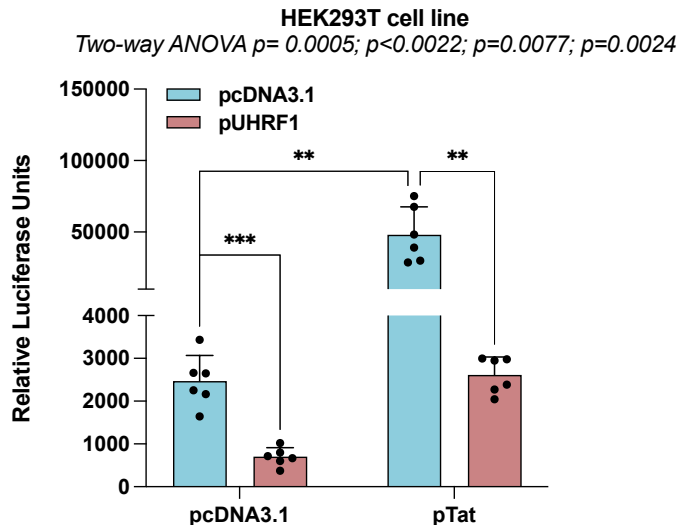
UHRF1 represses HIV-1 transcription independently of epigenetics and Tat

M. Bendoumou and C. Van Lint, unpublished data

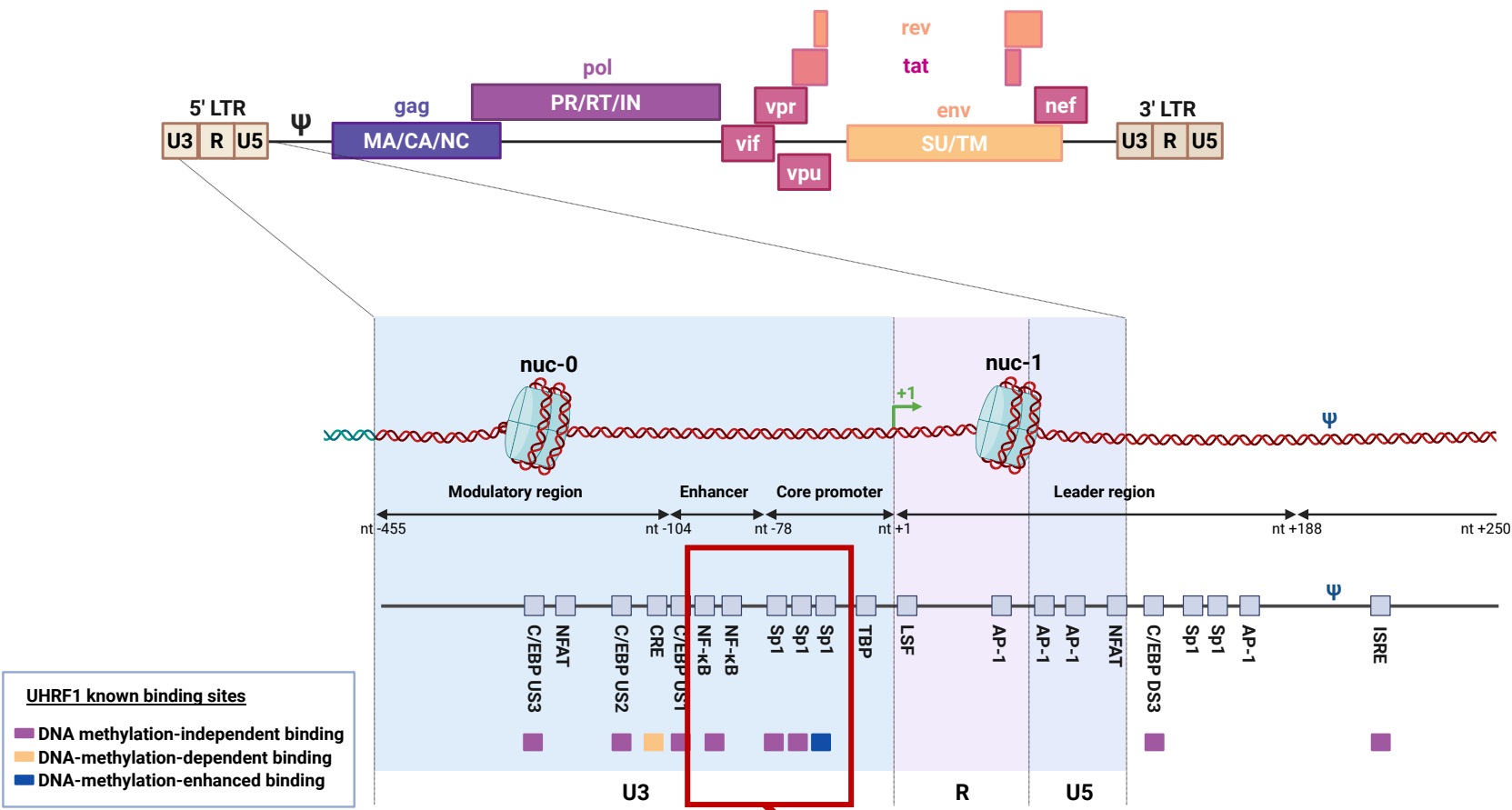
Epigenetic-free context



Tat-free context



DNA-methylation independent recruitment to Sp1 and NF-κB

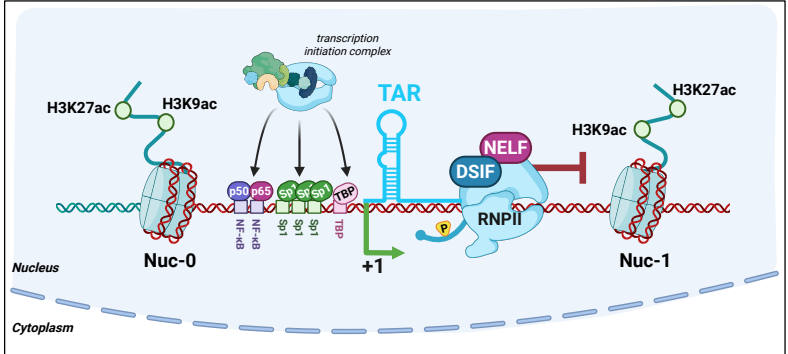


(Verdikt and Bendoumou et al, Ebiomedicine 2022)

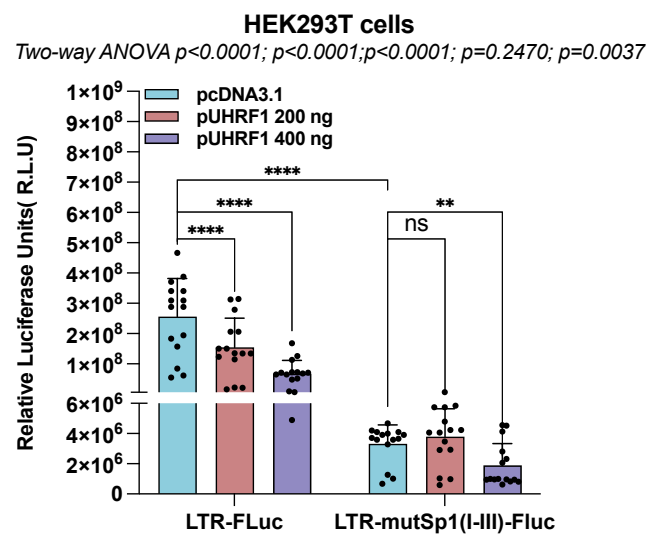
Critical for HIV-1 transcription

UHRF1 affects HIV-1 transcription initiation by interacting and inducing the degradation of Sp1 and NF-κB

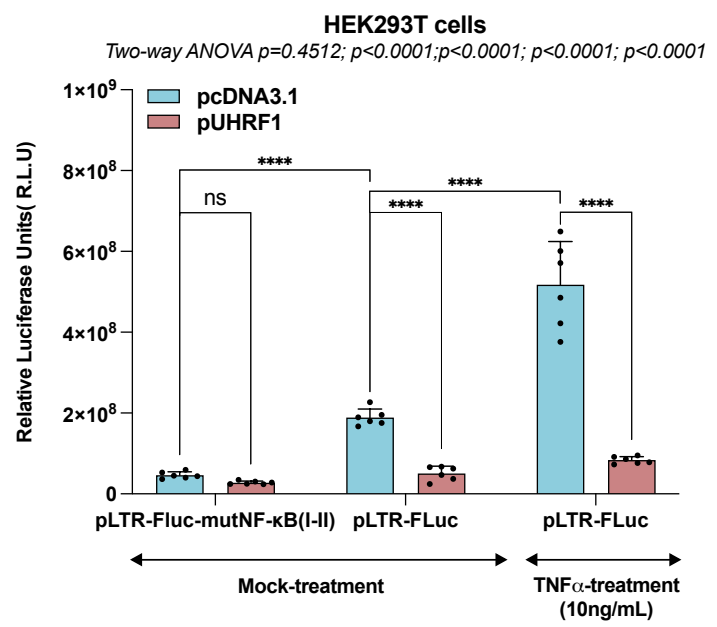
2. Transcriptional initiation



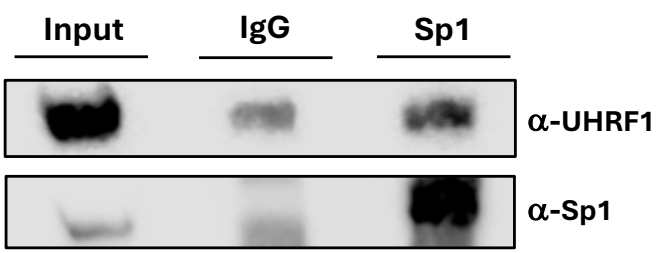
Repression in absence of Sp1



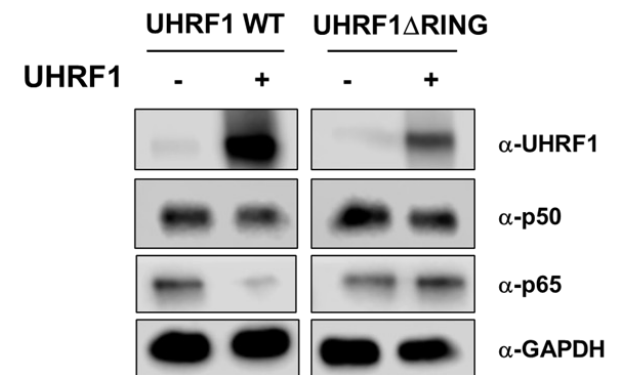
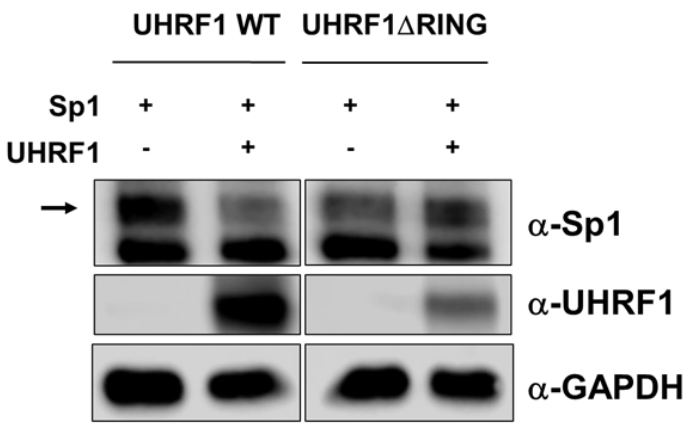
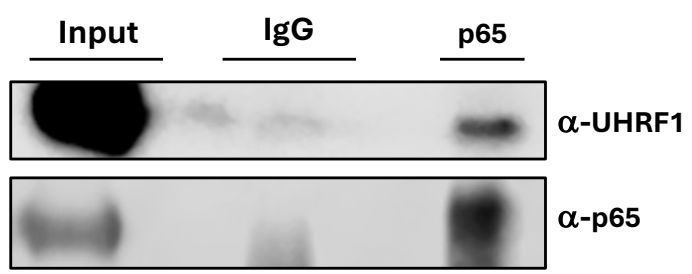
Repression in absence of NF-κB



Interaction of UHRF1 with Sp1 and NF-κB

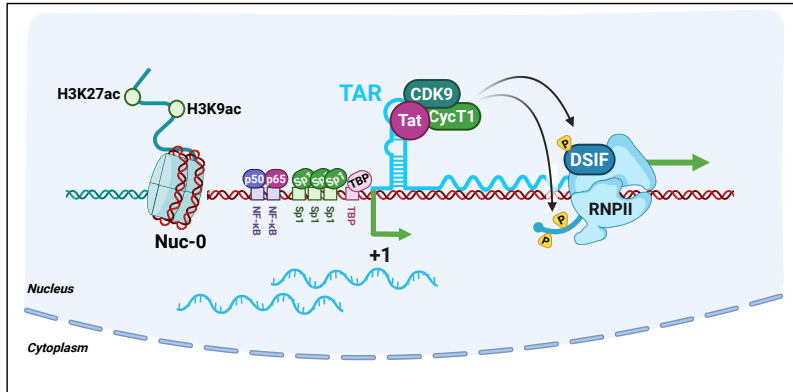


UHRF1 degrades Sp1 and p65 through its E3 ubiquitin activity



UHRF1 affects Tat-dependant and Tat-independent HIV-1 transcription elongation

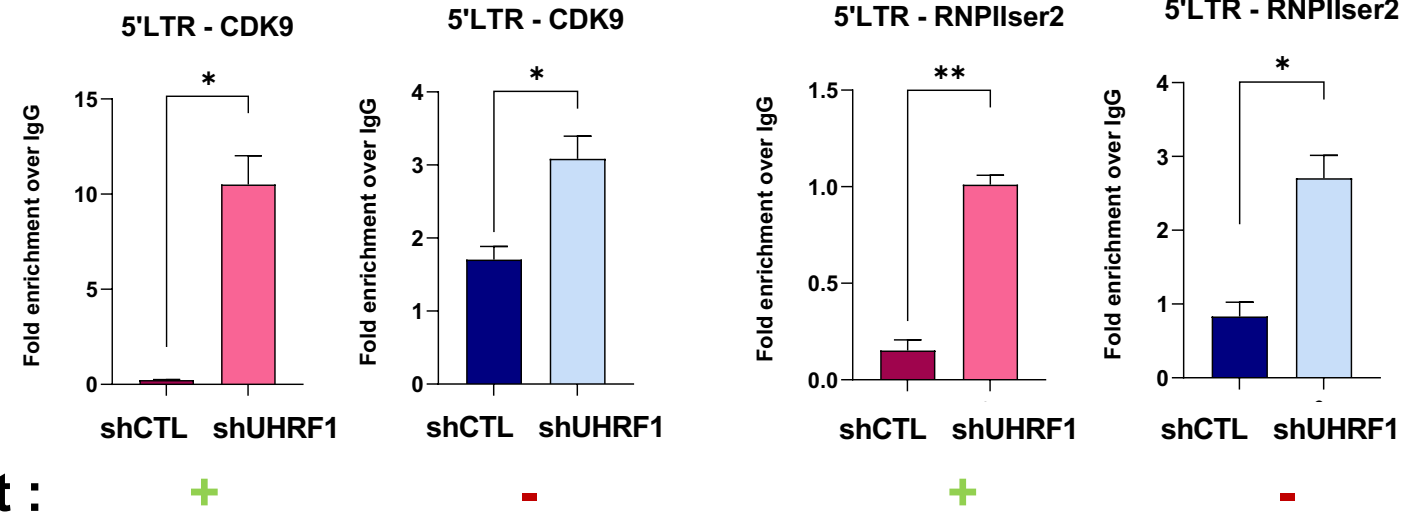
3. Transcriptional elongation



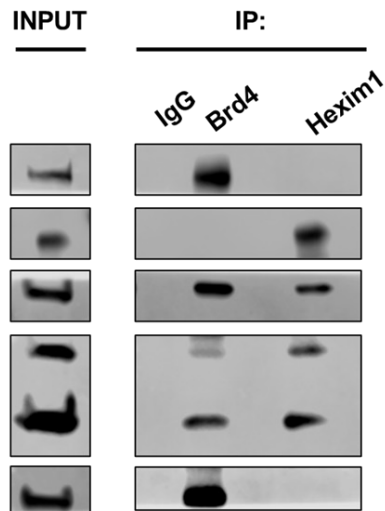
UHRF1 affects HIV-1 transcription elongation regardless of Tat presence

P-TEFb

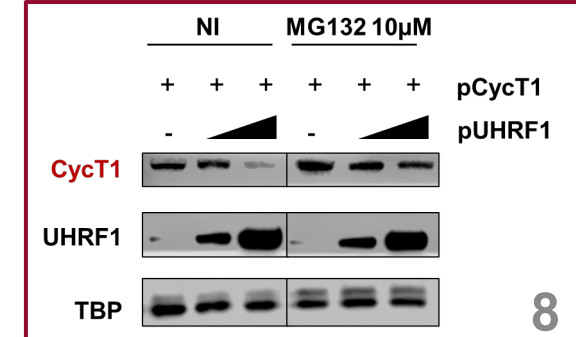
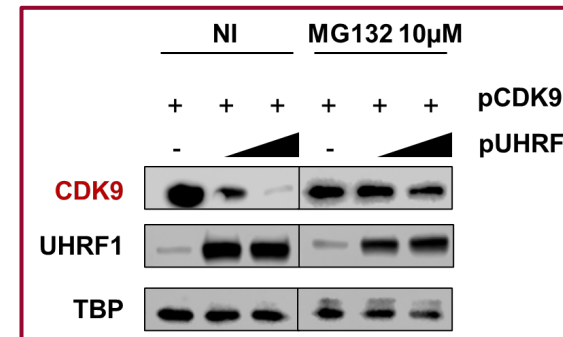
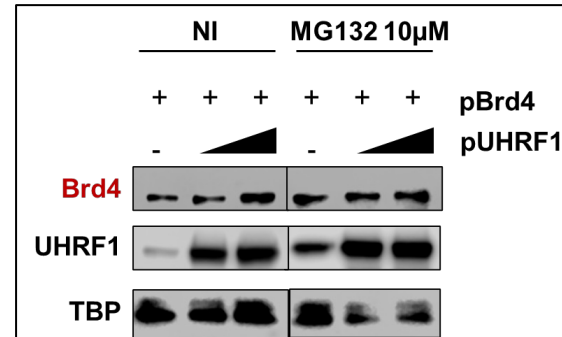
Elongating Pol II



UHRF1 interacts with the active P-TEFb complex

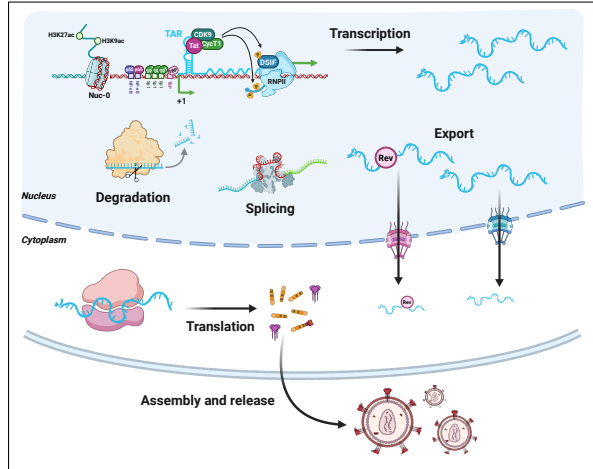


UHRF1 targets CDK9 and CycT1 subunits of P-TEFb for proteasomal degradation



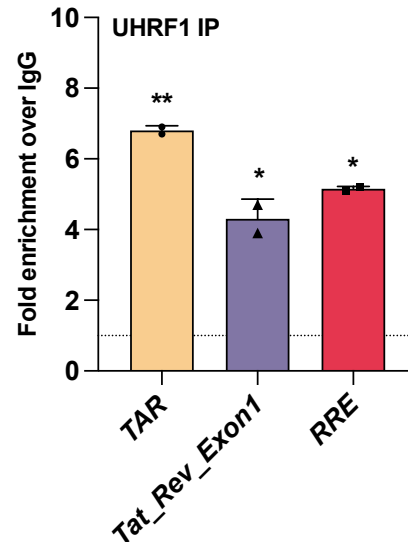
UHRF1 interacts with HIV-1 RNA and represses splicing and export

4. Post-transcriptional regulation

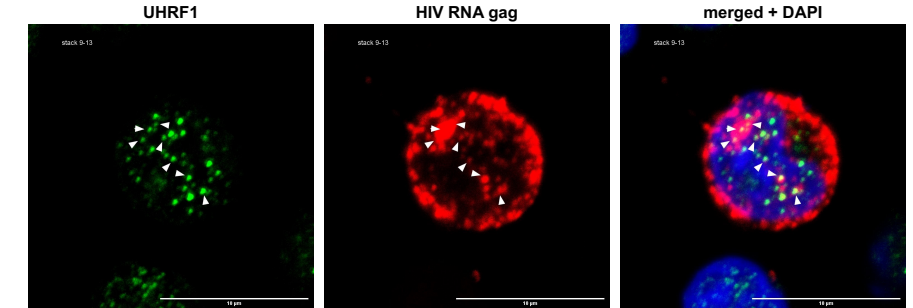


UHRF1 interacts HIV-1 RNA

Primary CD4⁺ T cells
Two-way ANOVA $p=0.006$; $p=0.018$; $p=0.014$



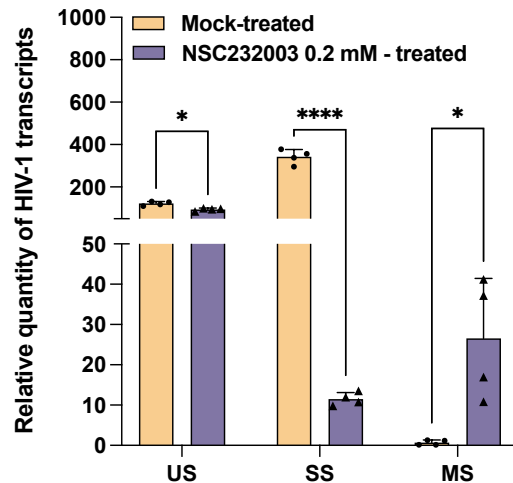
UHRF1 colocalizes with HIV-1 RNA



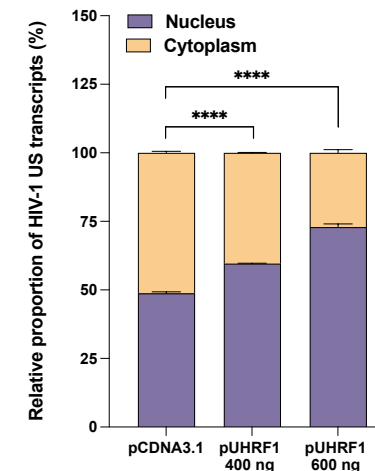
UHRF1 overexpression induce retention of Rev-dependant and -independent HIV-1 RNA

UHRF1 inhibition promotes splicing

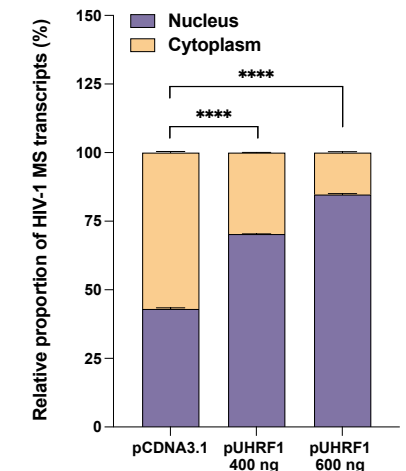
Primary CD4⁺ T cells
Two-way ANOVA $p=0.026$; $p<0.0001$; $p=0.037$



HEK293T cell line
Rev-dependent export (US HIV-1 RNA)
Two-way Anova $p<0.001$; $p<0.001$



HEK293T cell line
Rev-independent export (MS HIV-1 RNA)
Two-way Anova $p<0.001$; $p<0.001$

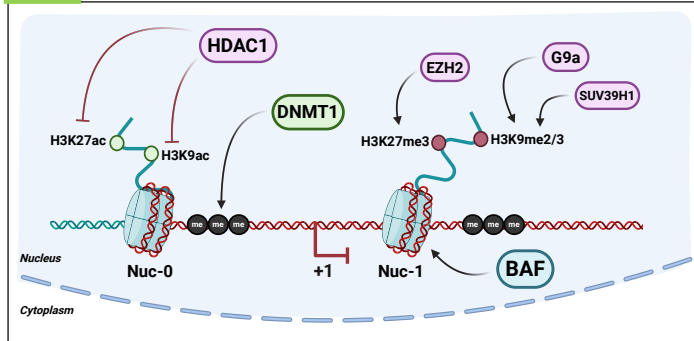


UHRF1 affects all blocks to HIV-1 gene expression and therefore constitutes a promising target for innovative cure strategies

UHRF1



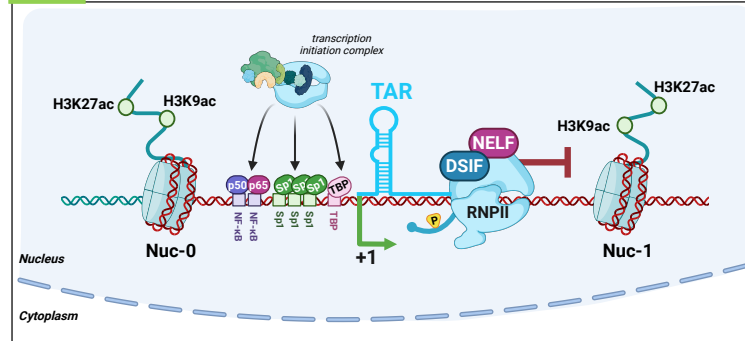
1. Epigenetically silent provirus



UHRF1



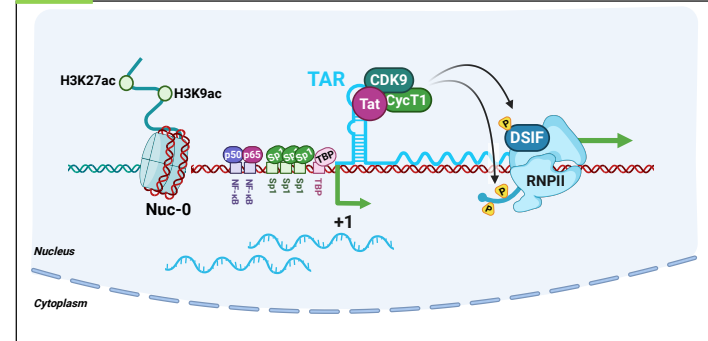
2. Transcriptional initiation



UHRF1



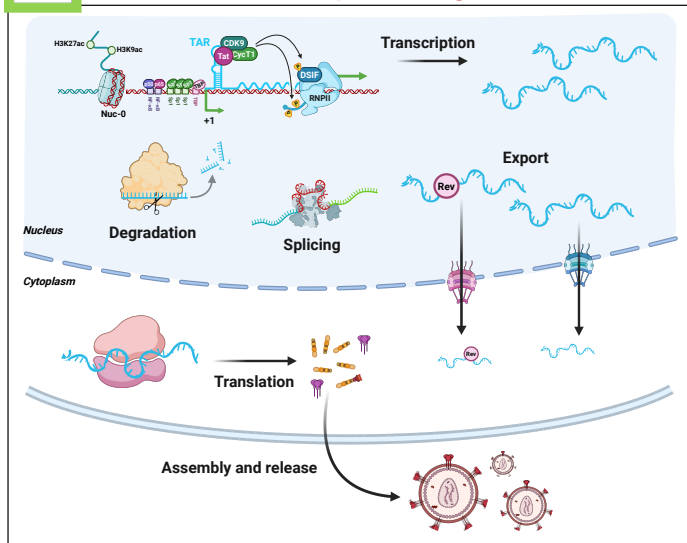
3. Transcriptional elongation



UHRF1



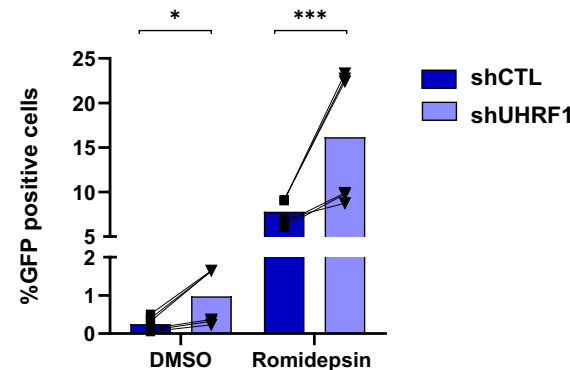
4. Post-transcriptional regulation



Downregulation of UHRF1 expression potentiates LRA-mediated reactivation of HIV-1

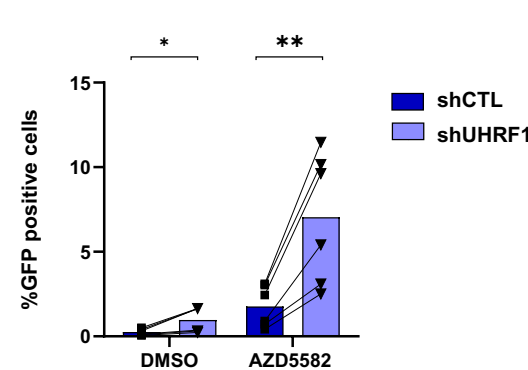
Epigenetics (HDACi)

Fold Synergy : (1.76 ± 0.42)



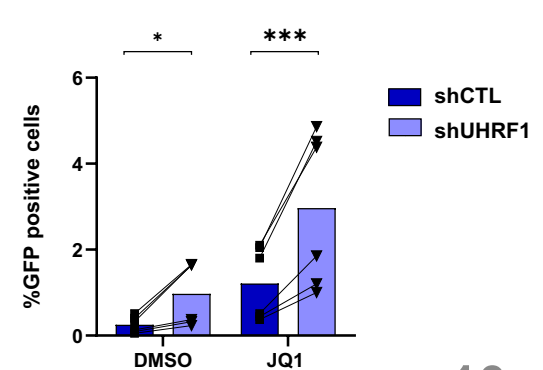
Transcription initiation (SMACm)

(2.97 ± 0.94)



Transcription elongation (BETi)

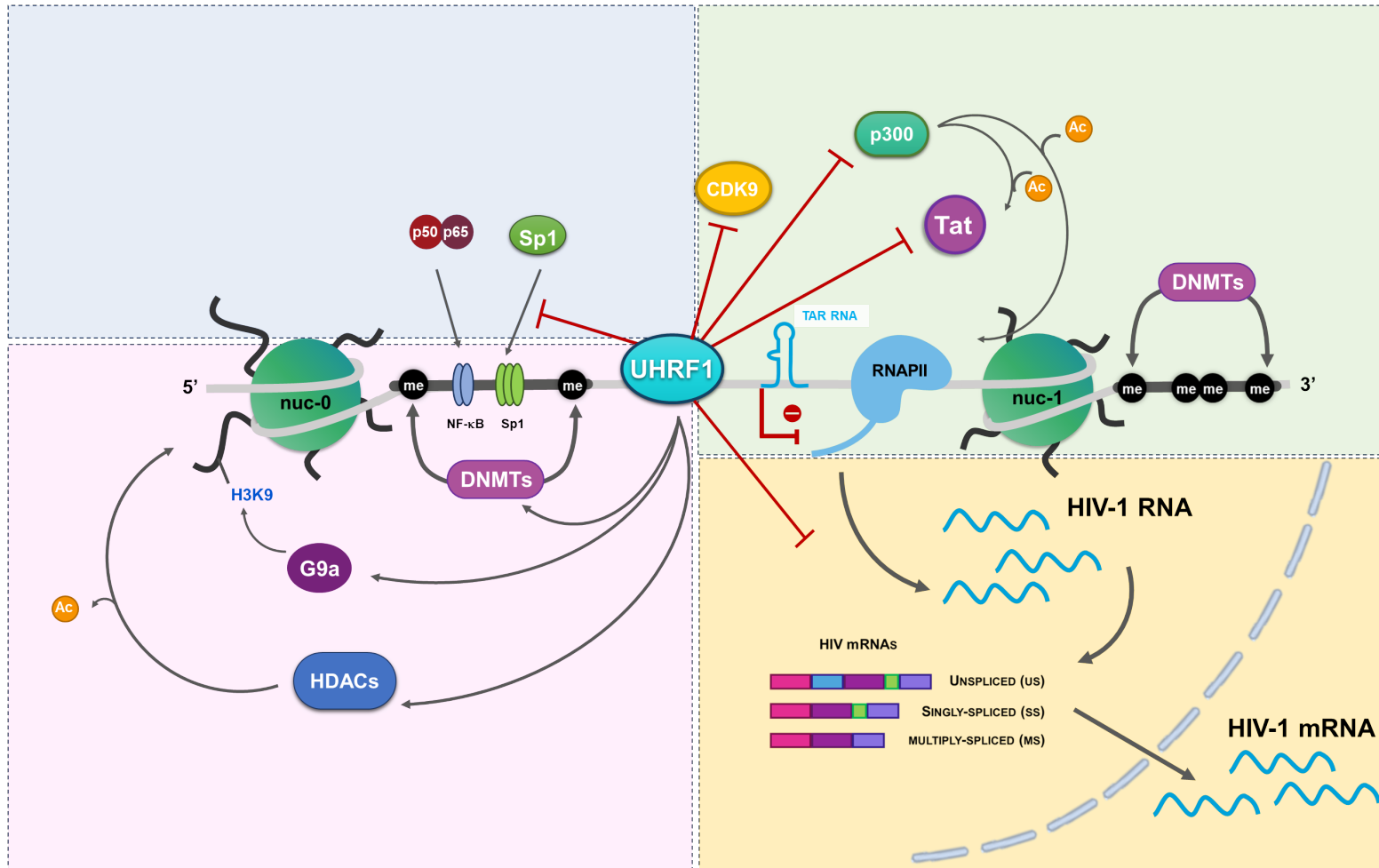
(1.54 ± 0.34)



Take home message

(2) Transcriptional initiation blocks

(3) Transcriptional elongation blocks



UHRF1 appears to be an important regulator of HIV-1 gene expression by acting on several checkpoints: at the epigenetic and at the transcriptional initiation and elongation levels pre- and post-Tat expression through its E3-ubiquitin ligase activity. Importantly, UHRF1 also affects HIV-1 gene expression at the post-transcriptional level. This poses UHRF1 as an attractive therapeutic target.

(1) Epigenetic blocks

(4) Post-transcriptional blocks

Thank you !



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