BREACH
BELGIAN RESEARCH AIDS&HIV CONSORTIUM

10th BREACH Symposium – Dolce La Hulpe
Wednesday, November 23rd, 2022

ROLE OF UHRF1 IN HIV-1 TRANSCRIPTIONAL REGULATION

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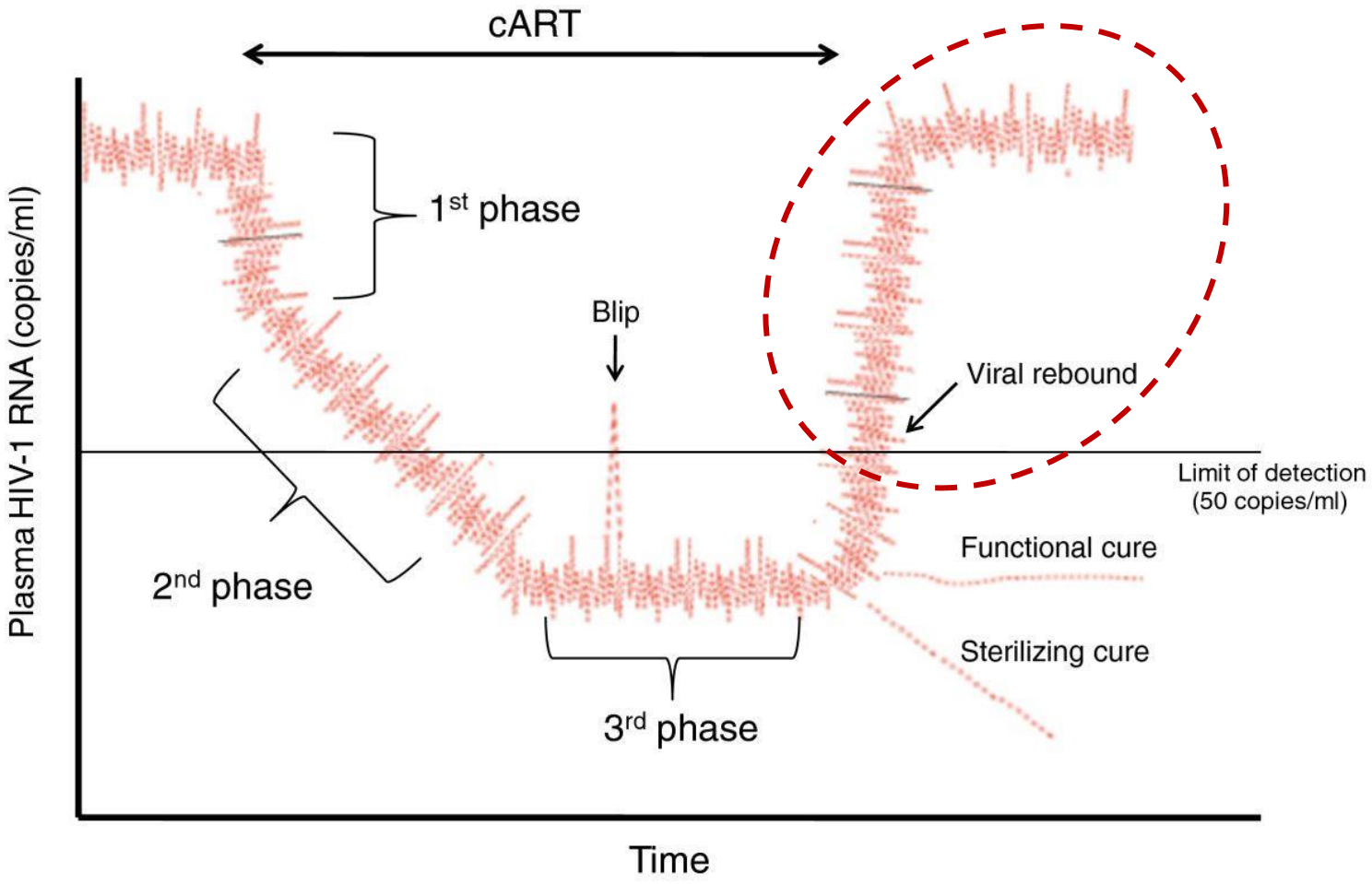
LABORATORY OF MOLECULAR VIROLOGY (ULB)

HEAD : PR. CARINE VAN LINT

ULB UNIVERSITÉ LIBRE DE BRUXELLES

ULB Service of Molecular Virology

COMBINATION ANTIRETROVIRAL THERAPY (cART) IS POTENT AND LIFE-PROLONGING BUT DOES NOT ERADICATE HIV INFECTION



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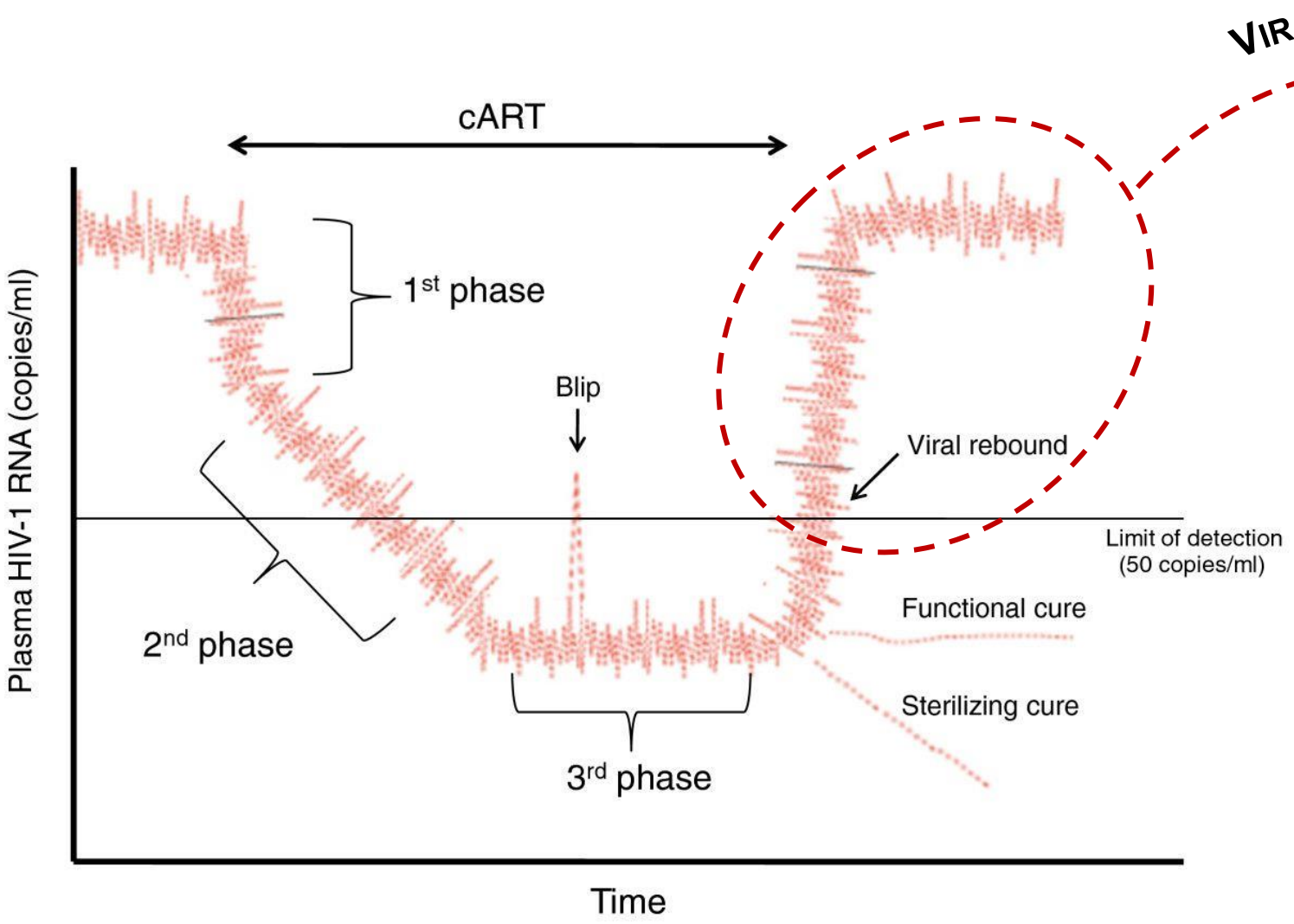

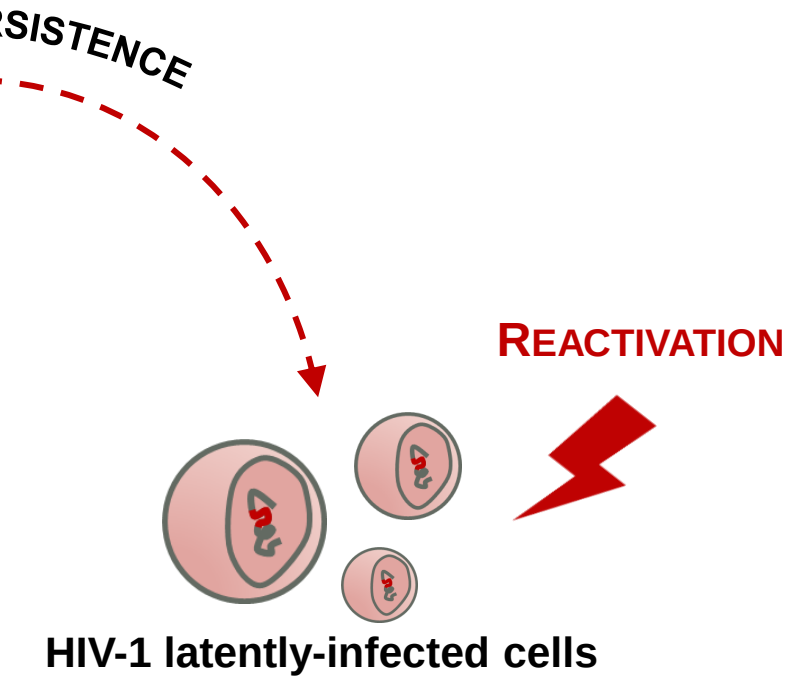

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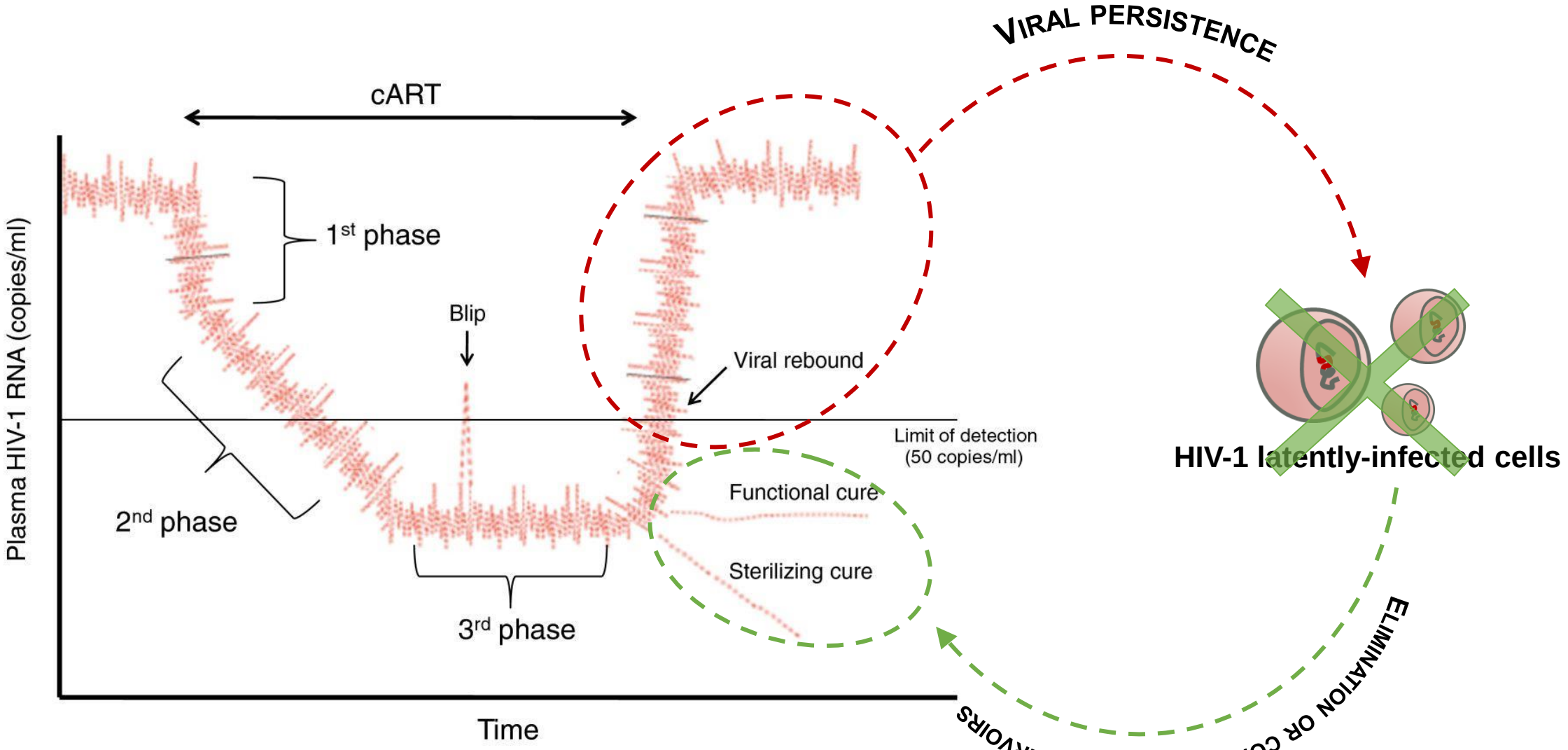
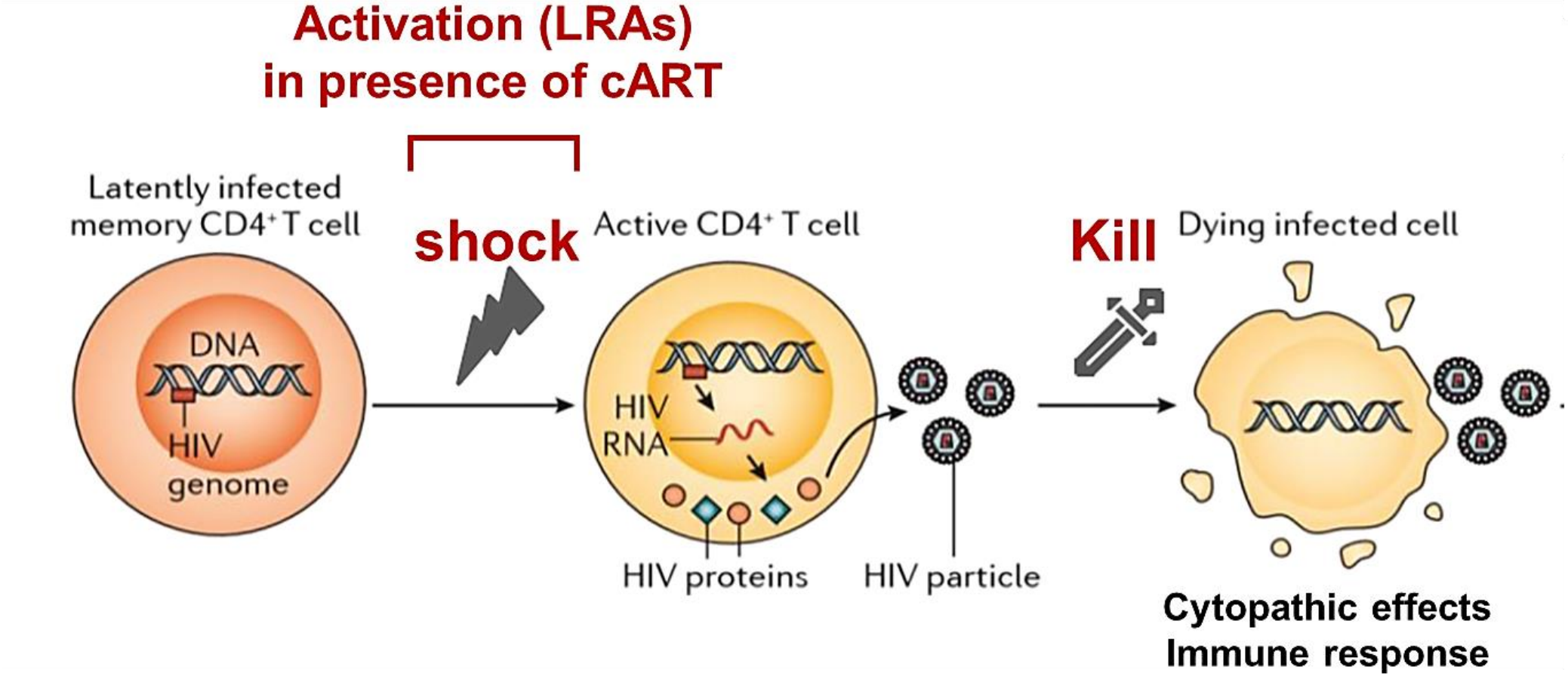
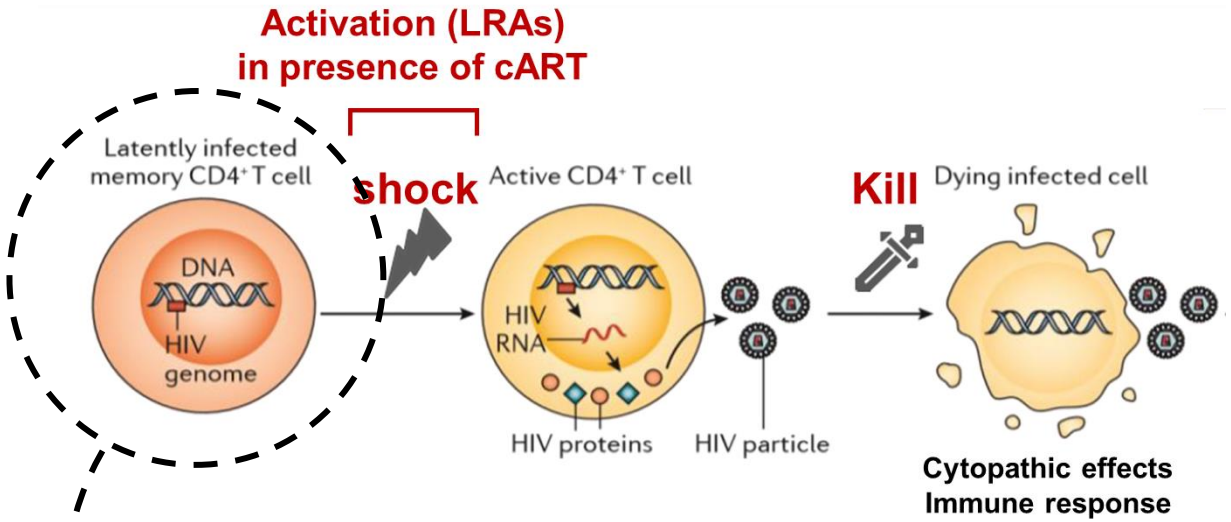


THE « SHOCK AND KILL » STRATEGY FOR PURGING LATENT VIRAL RESERVOIRS IS ONE OF THE MOST EXPLORED APPROACHES IN REACHING A CURE FOR HIV



(S. Deeks *et al*., Nat,Review 2015)

UNDERSTANDING MOLECULAR MECHANISMS DRIVING HIV-1 LATENCY IS ESSENTIAL TO DEVELOP NEW CURE STRATEGIES



Understanding the mechanisms driving HIV-1 latency is the key to develop new LRAs

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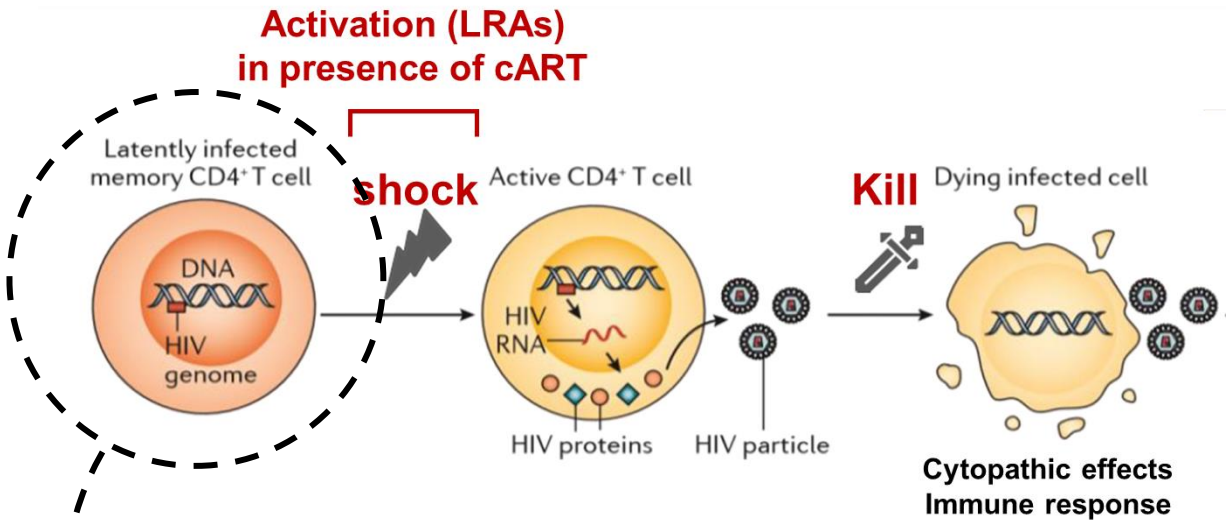

Understanding the mechanisms driving HIV-1 latency is the key to develop new LRAs

Epigenetic blocks
- DNA methylation
- Nucleosme positioning
- Histone PTMs (methylation, deacetylation)

Transcription initiation blocks
- Poor availability of positively acting TFs
- Abundance of negatively acting TFs

Transcription elongation blocks
- Negative elongation F
- Absence of Tat
- Sequestration of active P-TEFb

Post-transcriptional blocks
- Blocks to splicing
- Block to export
- Inhibitory miRNAs
- Translation blocks

BLOCKS TO HIV-1 GENE EXPRESSION

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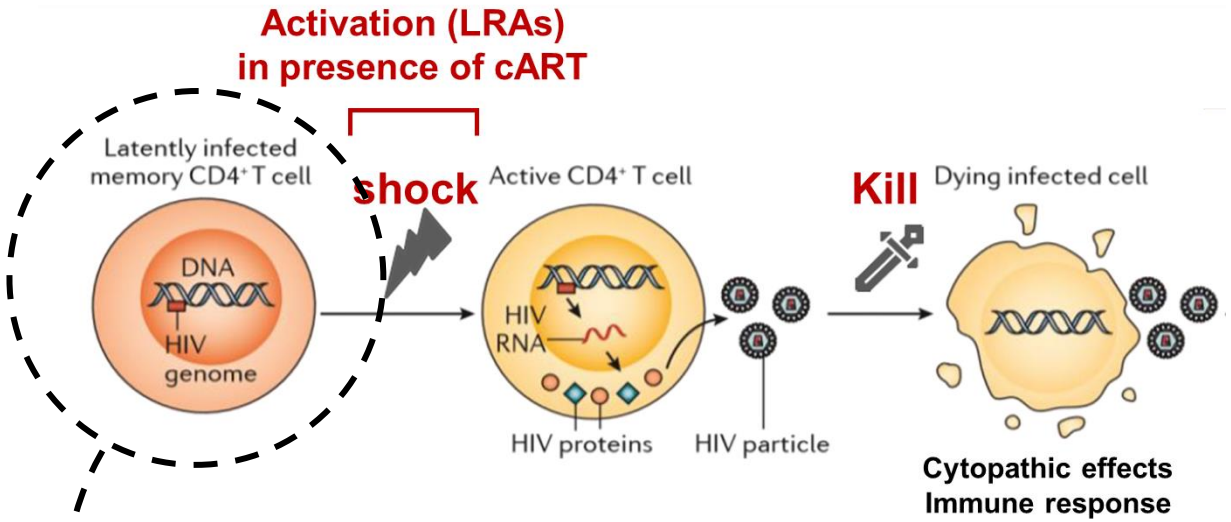

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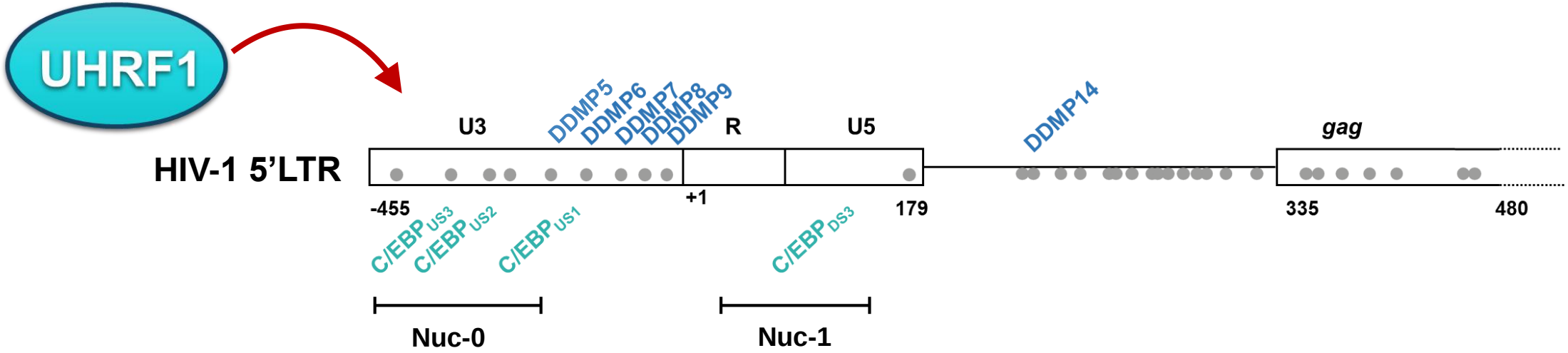
BLOCKS TO HIV-1 GENE EXPRESSION

UHRF1 IS RECRUITED *IN VIVO* TO HIV-1 LATENT PROMOTER



(Bendoumou *et al.*, eBioMedicine 2022)

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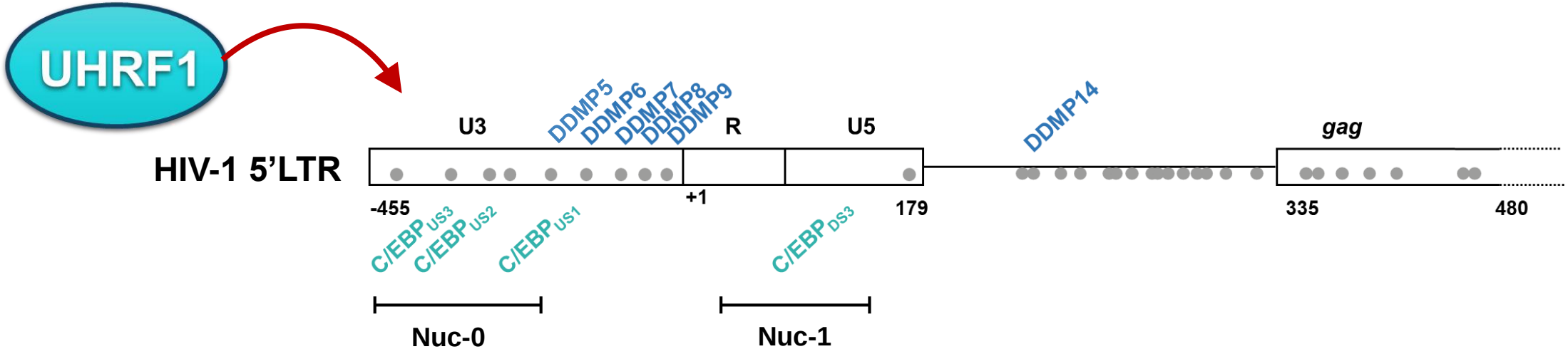
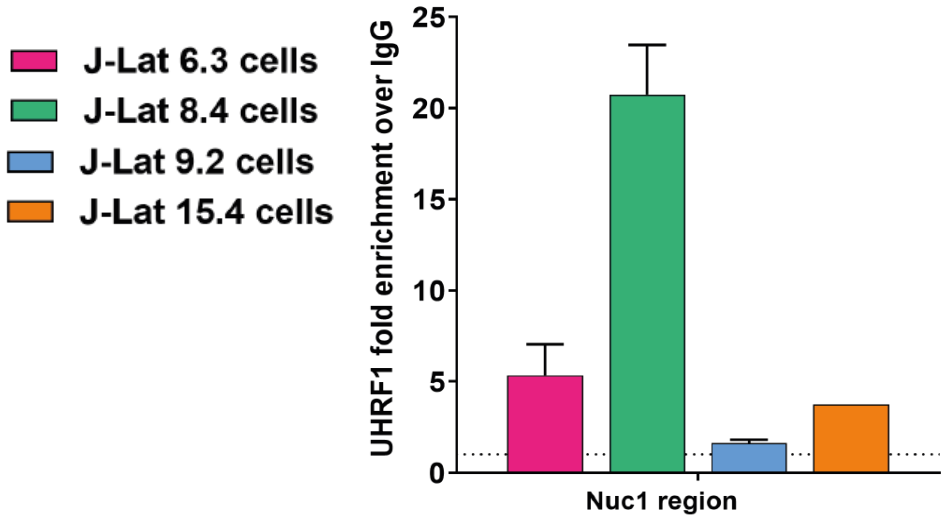
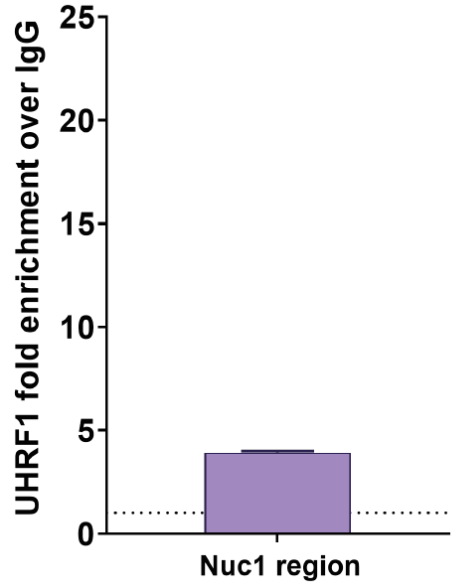


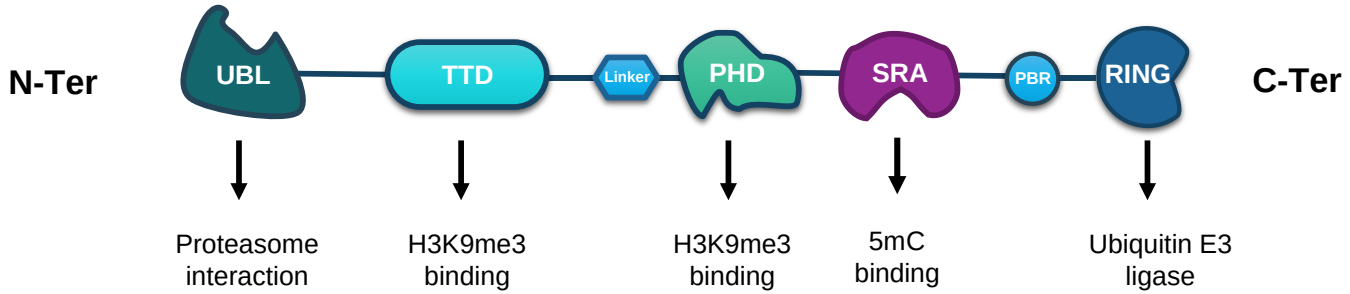


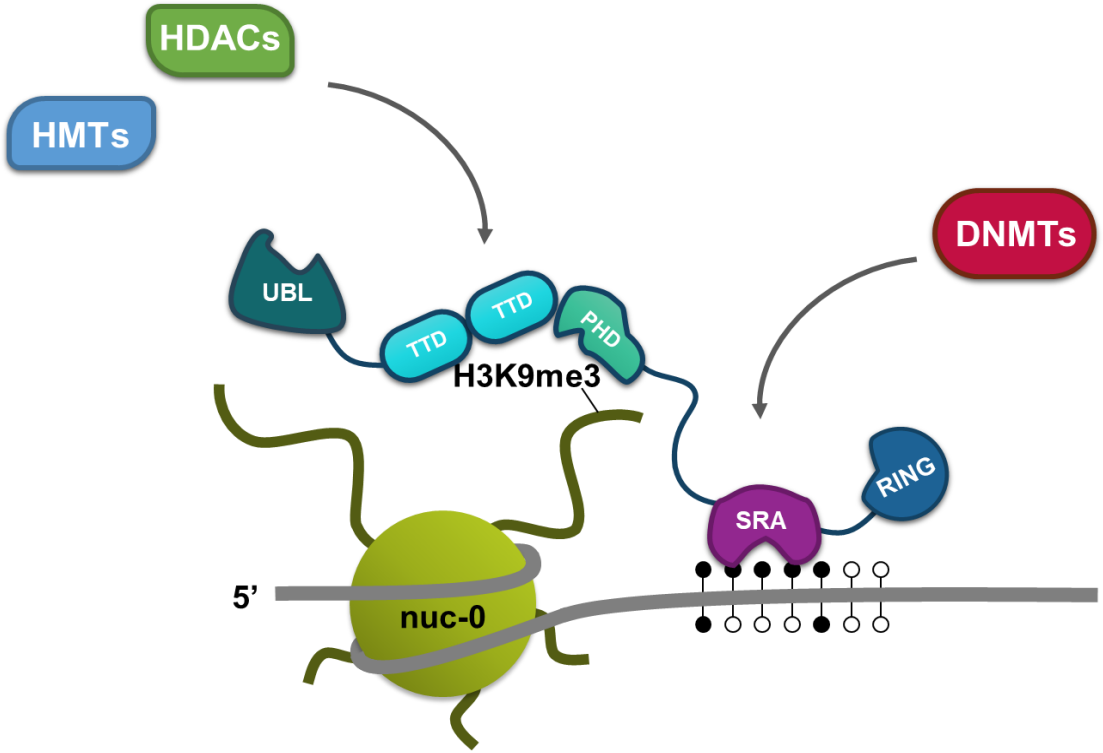


(Bendoumou *et al.*, eBioMedicine 2022)

UHRF1 IS RECRUITED *IN VIVO* TO HIV-1 LATENT PROMOTER

UHRF1: Ubiquitin-like containing PHD and RING Finger domains 1





ESSENTIAL FOR MAINTENANCE OF HETEROCHROMATIN PROFILES DURING REPLICATION

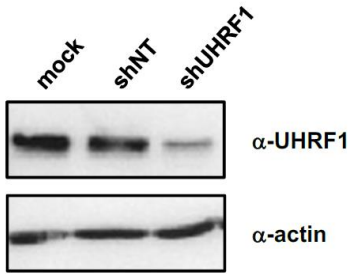
↓

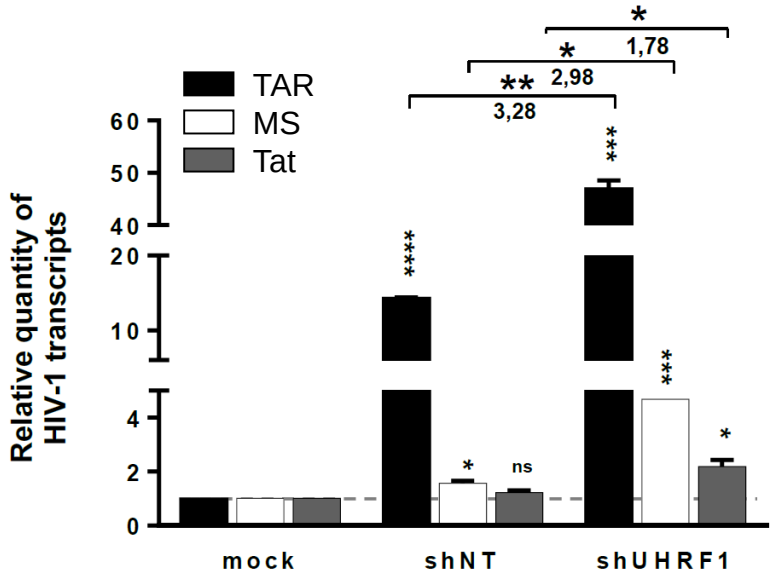
HIV-1 ?

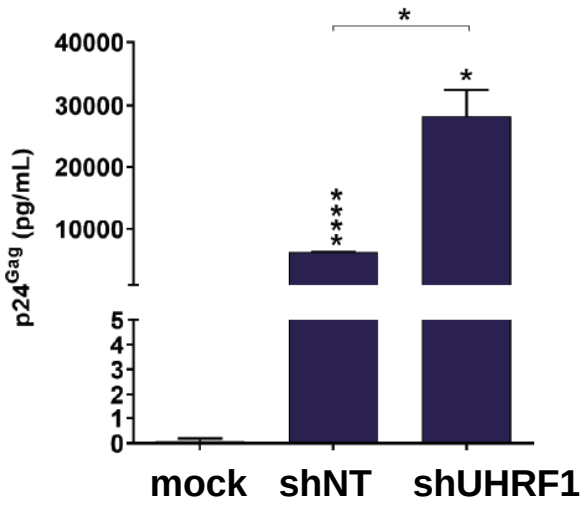
(Bendoumou *et al.*, eBioMedicine 2022)

UHRF1 KNOCKDOWN INDUCES HIV-1 REACTIVATION FROM LATENCY

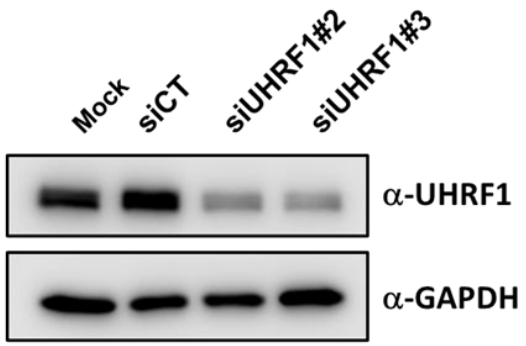
J-LAT 8.4

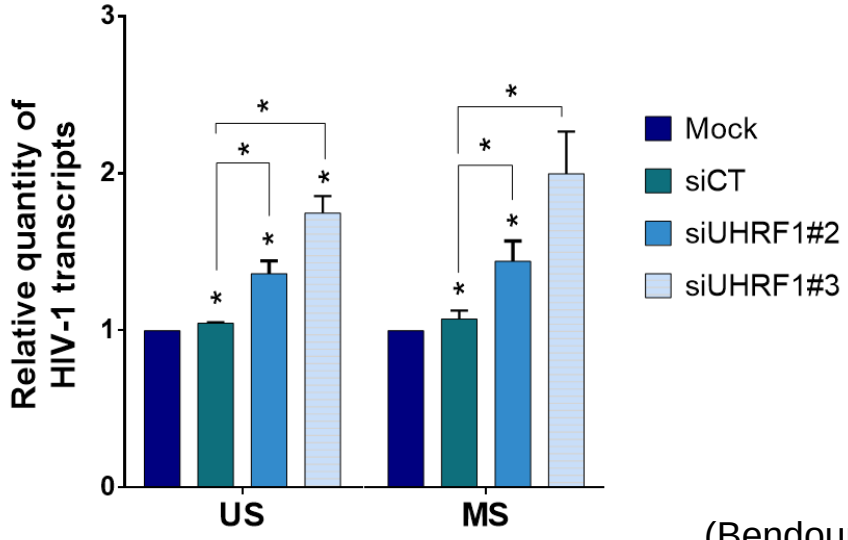






PRIMARY CD4+ T CELL MODEL

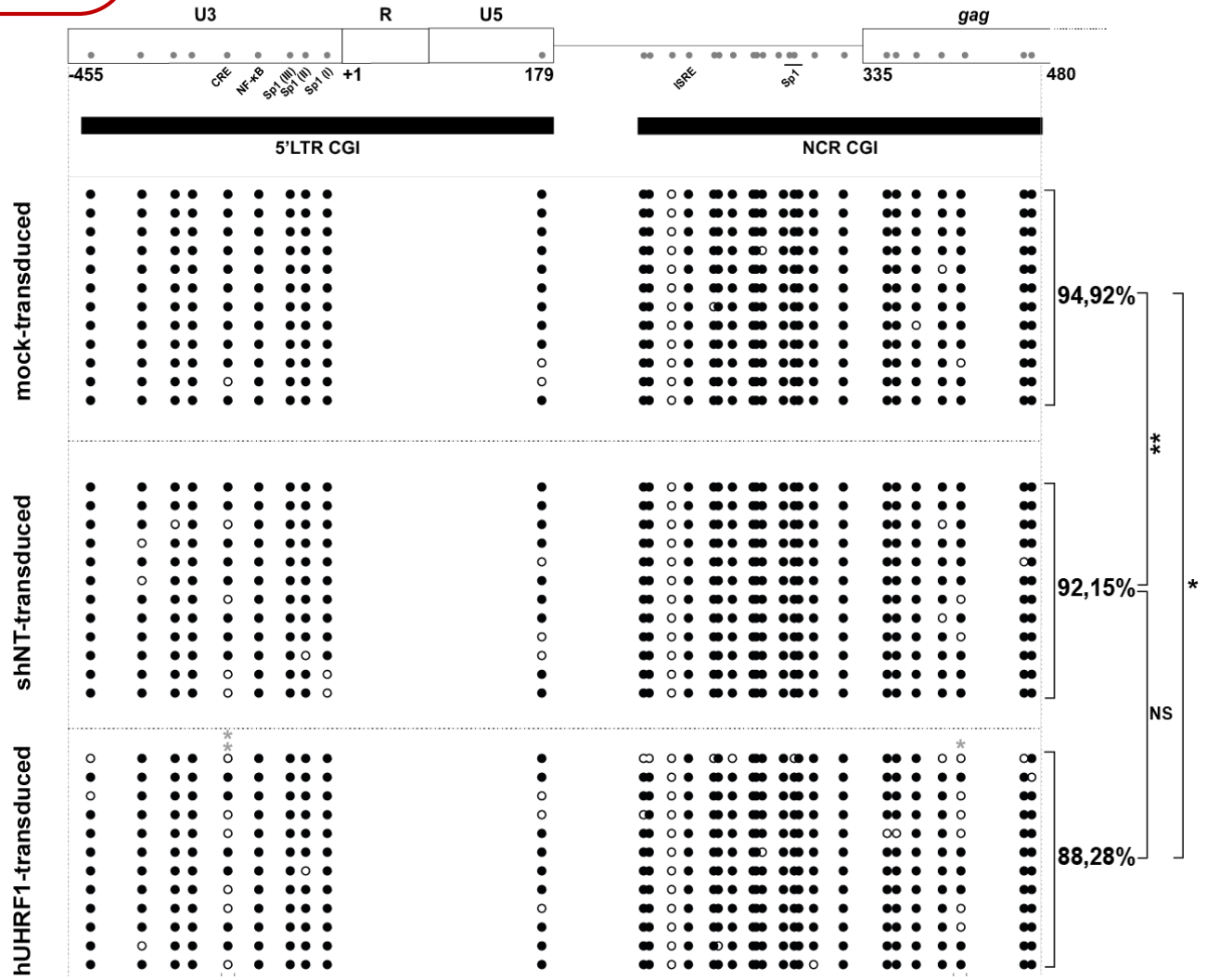


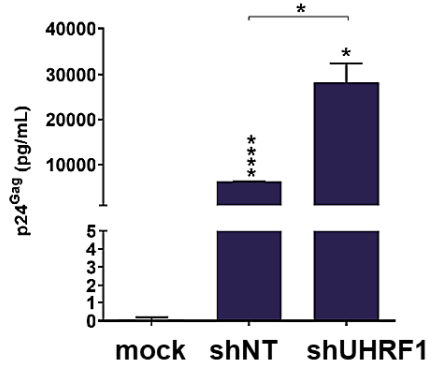


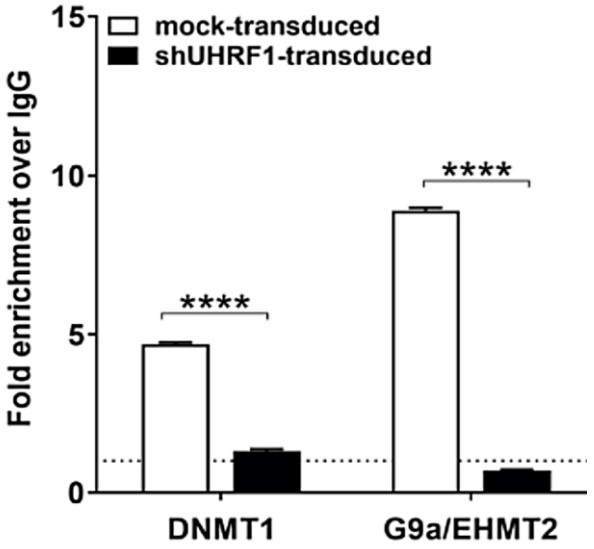
(Bendoumou *et al.*, eBioMedicine 2022)

UHRF1 KNOCKDOWN CELLS INDUCES A GLOBAL 5' LTR DEMETHYLATION IN J-LAT 8.4

J-LAT 8.4



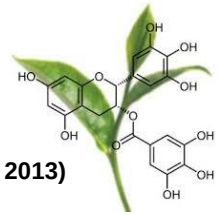




(Bendoumou *et al.*, eBioMedicine 2022)

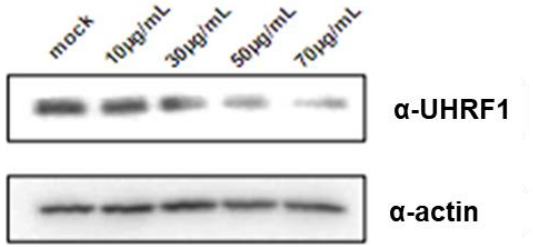
PHARMACOLOGICAL INHIBITION OF UHRF1 INDUCES HIV-1 REACTIVATION

UHRF1 ⊣ **EpiGalloCatechin-3-Gallate (EGCG)**



(Achour *et al.*, Biochem. Biophys. Res. Commun. 2013)

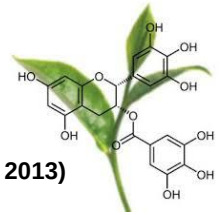
J-LAT 8.4 CELLS



(Bendoumou *et al.*, eBioMedicine 2022)

EGCG INDUCES HIV-1 GENE EXPRESSION IN *EX VIVO* CULTURES OF CD8+-DEPLETED PBMCS ISOLATED FROM ART-TREATED AVIREMIC HIV+ PATIENTS

UHRF1 ⊣ EpiGalloCatechin-3-Gallate (EGCG)



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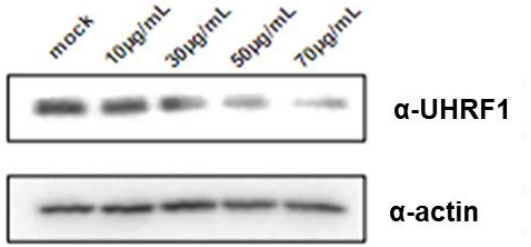
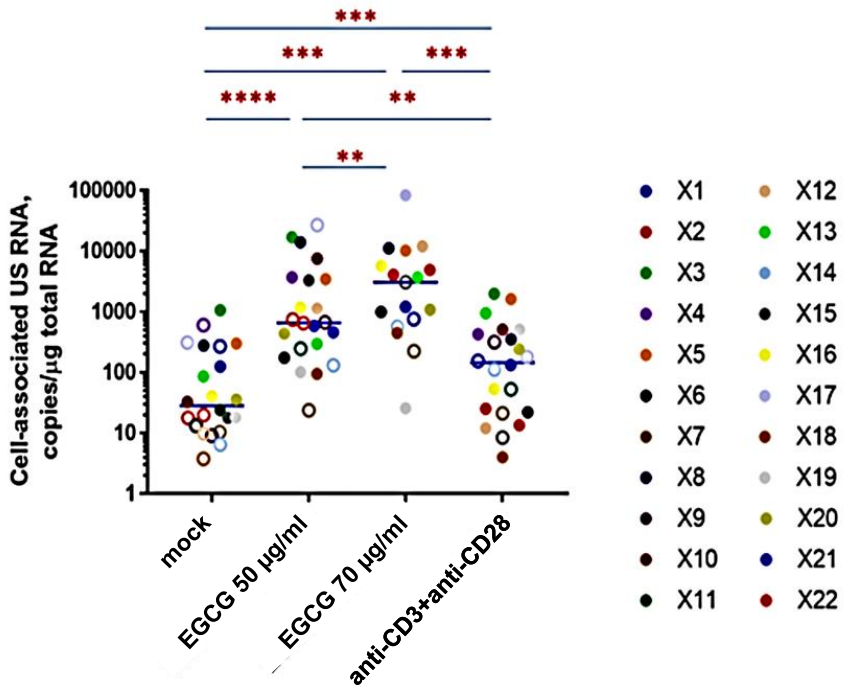


24H TREATMENT

Median level of HIV-1 intracellular US RNAs



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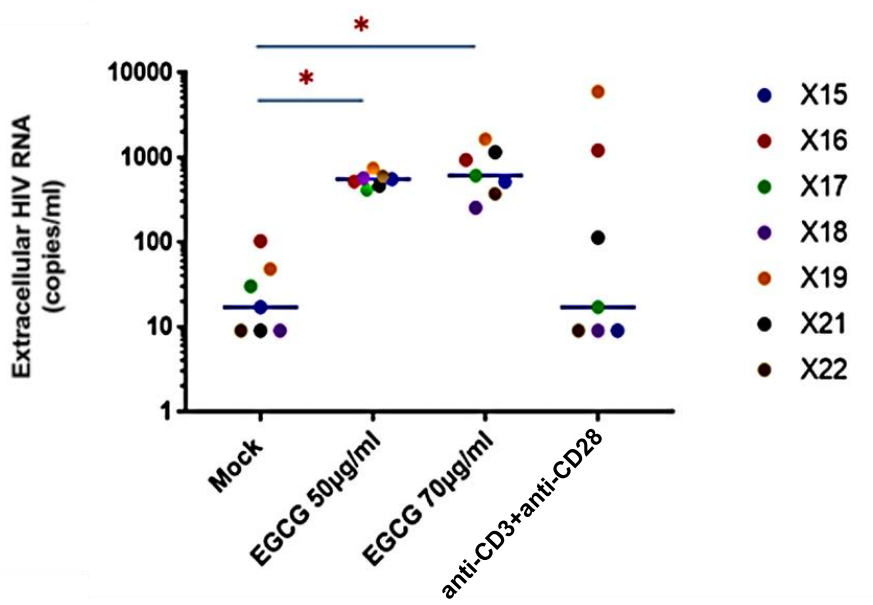
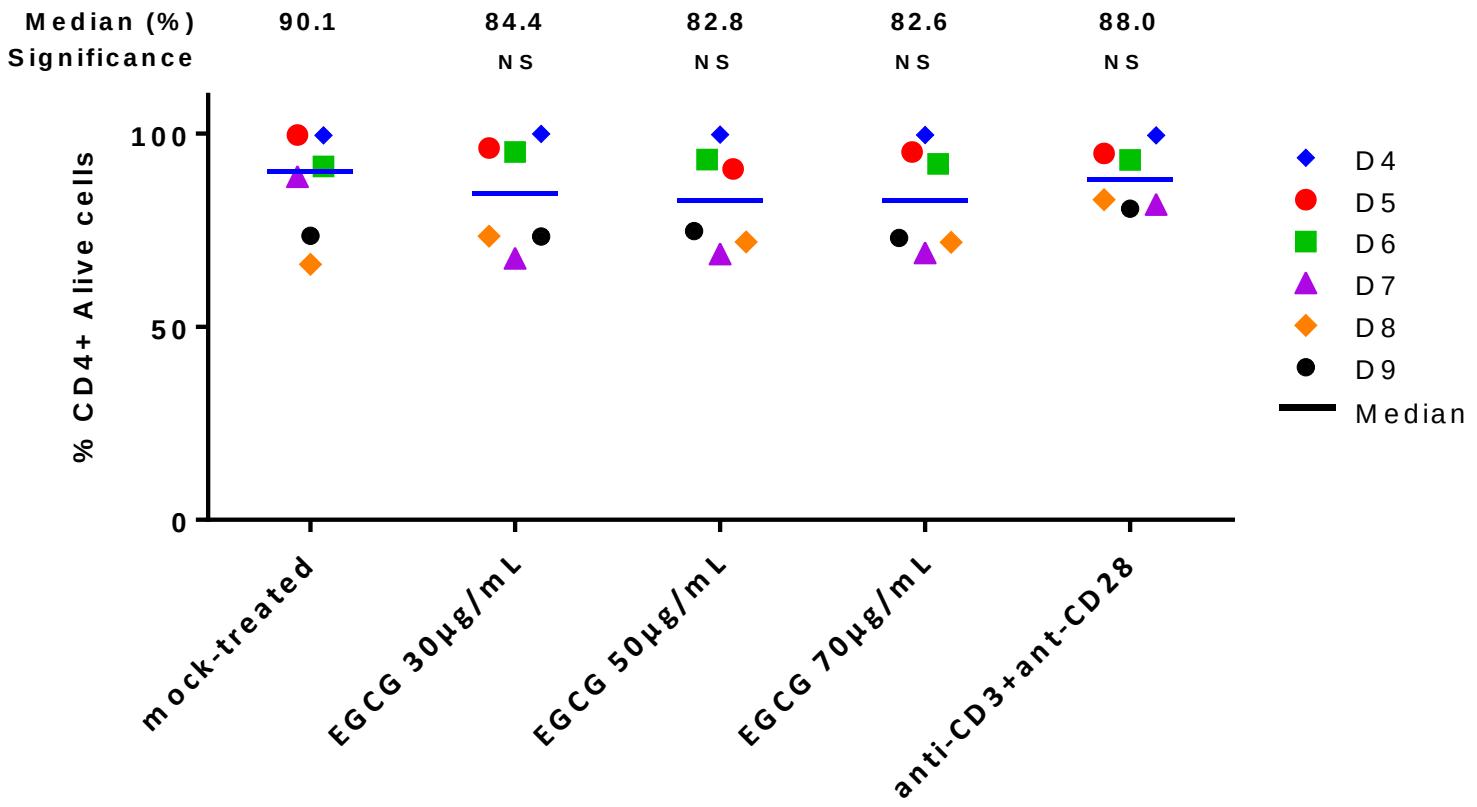


(Bendoumou *et al.*, eBioMedicine 2022)

EGCG DOES NOT AFFECT CELLULAR VIABILITY

LIVE/DEAD STAINING

24H stimulation of CD8-depleted PBMCs isolated from healthy donors

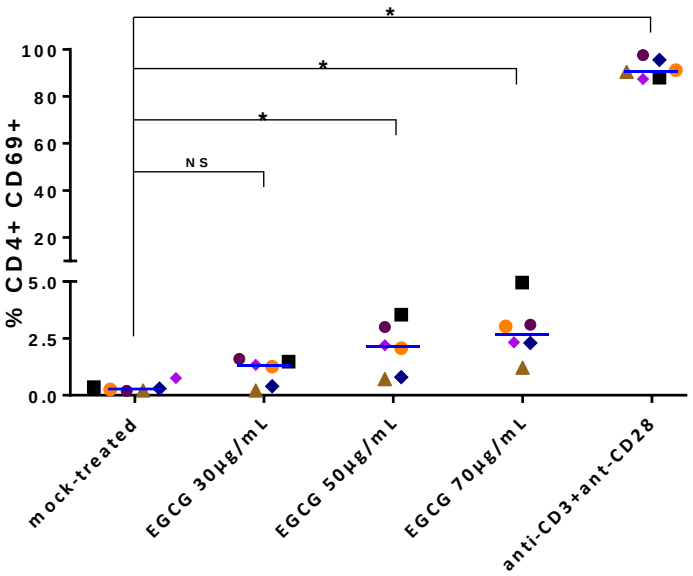


(Bendoumou *et al.*, eBioMedicine 2022)

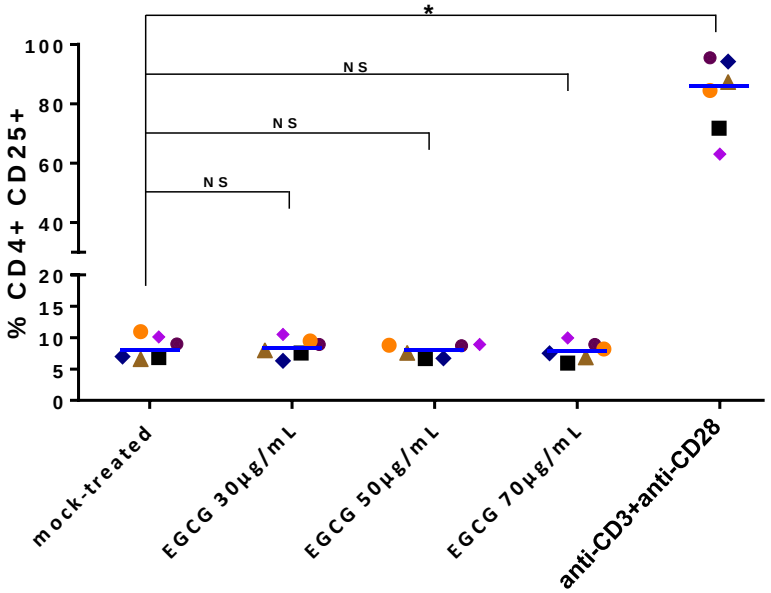
EFFECT OF EGCG ON T CELL ACTIVATION

24H

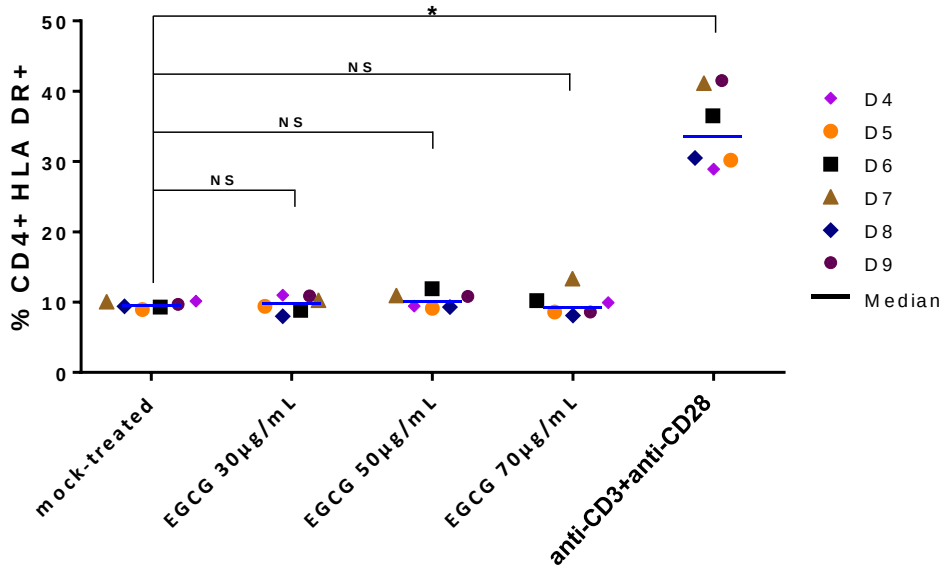
EARLY (CD69)



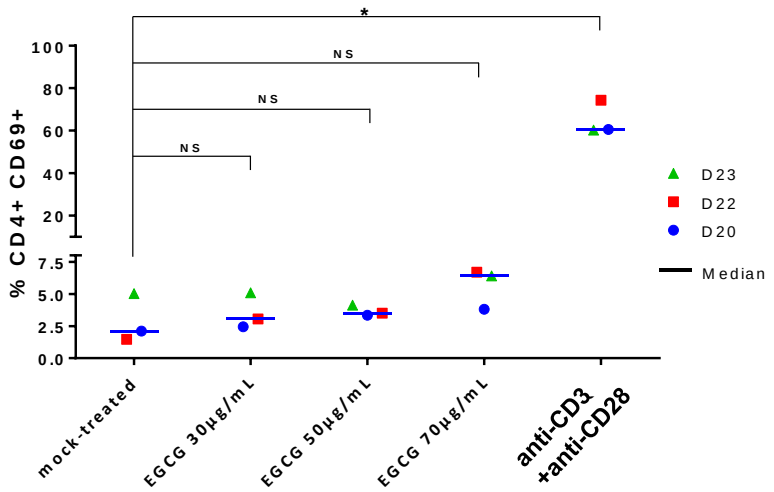
INTERMEDIATE (CD25)



LATE (HLA DR+)



6 Days

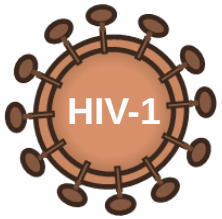


***Ex vivo* EGCG treatment reactivates HIV-1 expression without inducing a strong T cell activation.**

(Bendoumou *et al.*, eBioMedicine 2022)

EGCG IS A GOOD CANDIDATE FOR SHOCK AND KILL STRATEGY

EGCG



EARLY STEPS : RECEPTOR RECOGNITION

(Williamson *et al*, J Allergy Clin Immunol.2006)

REVERSE TRANSCRIPTION

(Li *et al*, Antivir.Chem.Chemother. 2011)

LATE STEPS : TRANSCRIPTION (Yang *et al*, EMBO Rep. 2020)

VIRAL PARTICLE STABILITY

(Yamaguchi *et al*, Antiviral Res. 2002)

REACTIVATES HIV-1 FROM LATENCY

(Bendoumou *et al.*, eBioMedicine 2022)

THE NATURAL COMPOUND **EGCG** APPEARS TO BE A PROMISING CANDIDATE FOR A "SHOCK AND KILL" STRATEGY, PROVOKING A TRANSCRIPTIONAL AND TRANSLATIONAL WAKE UP OF LATENTLY INFECTED CELLS WHILE MAINTAINING A SUPPRESSION OF VIRUS PRODUCTION AND REPLICATION.

CONCLUSION

- **We showed UHRF1 plays a functional role in the epigenetic repression of HIV-1 transcription through both DNA methylation-dependent and -independent mechanisms, such as histone methylation.**
- **Therefore, UHRF1 could constitute a new therapeutic target anti-HIV cure strategies.**
- **The pharmacological UHRF1 inhibitor EGCG reactivates HIV-1 gene expression in *ex vivo* $CD8^+$-depleted PBMCs cultures from cART-treated aviremic HIV^+ patients :**
  - **Without impacting viability of CD4+ cells.**
  - **Without inducing a strong T cell immune activation.**

+ Antiviral properties

EGCG IS AN ATTRACTIVE LRA CANDIDATE

Acknowledgments

Study Participants

Laboratory of Experimental Virology, University of Amsterdam, The Netherlands

- Ben Berkhout
- Gilles Darcis
- Alexander Pasternak

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- Coca Necsoi

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- Bruno Verhasselt

HIV Cure Research Center, Department of General Internal Medicine, Ghent University Hospital, Ghent University, Belgium

- Linos Vandekerckhove

Service of Molecular Virology, University of Brussels (ULB), Belgium

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- Caroline Vanhulle
- Estelle Plant
- Tristan Marray
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- Mathilde Galais
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- Virginie Gautier
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- Asier Saez-Cirion
- Caroline Pereira Bittencourt Passaes
- Valérie Monceaux
- Annie David

Necker Hospital, Paris, France

- Christine Rouzioux
- Véronique Avettand-Fenoël

NIH National Institutes of Health
ERASE HIV
Martin Delaney Collaboratories for HIV Cure Research
NIAID/NHLBI/NIDDK/NINDS/NIDA UM1AI164562

ViiV Healthcare

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HIViera
Remission of HIV infection era

RÉGION WALLONNE

Fondation Roi Baudouin
Agir ensemble pour une société meilleure