

# Durable Control of Viral Rebound in Humanized Mice by ABX464 Targeting Rev Functions

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*J. TAZI received research grants awarded to his institution from ABIVAX, has served as consultant to ABIVAX and owns stock in ABIVAX*



# PremRNA splicing a major contributor of protein diversity

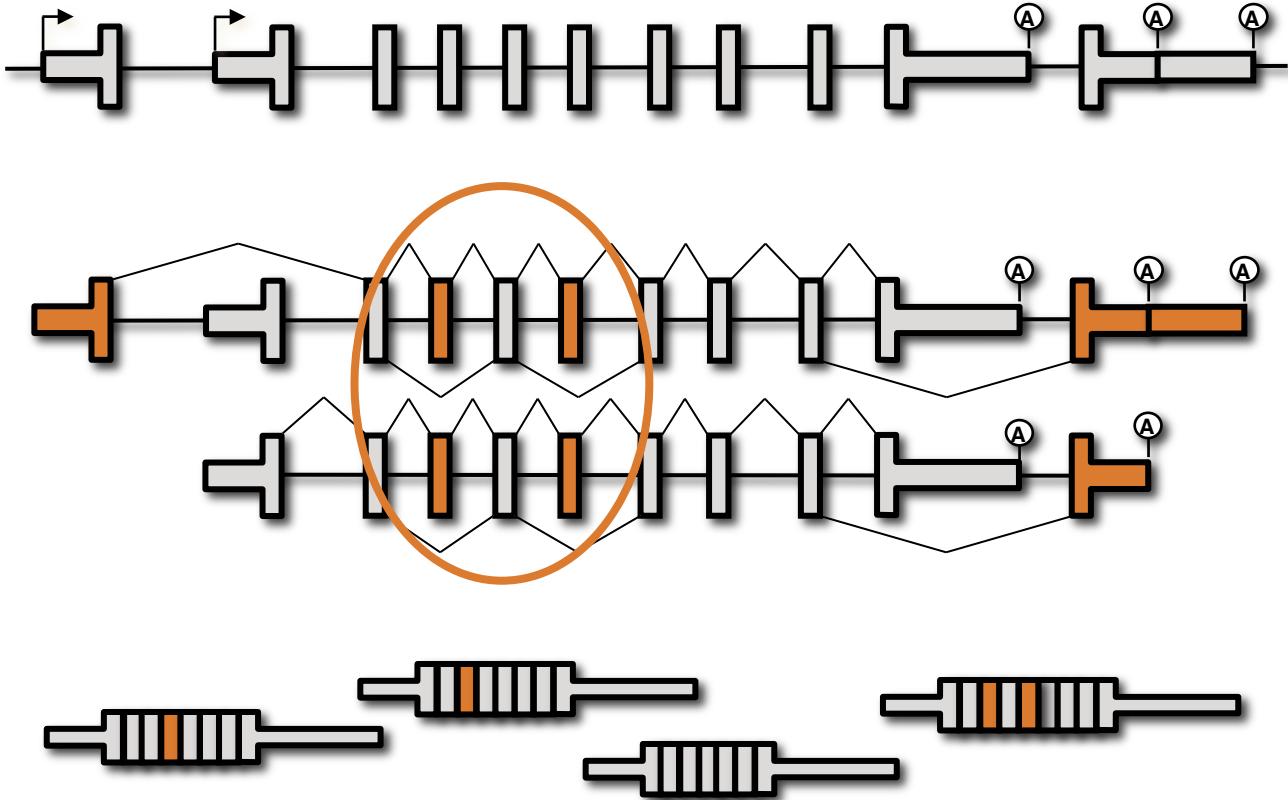
Gene



pre-mRNAs



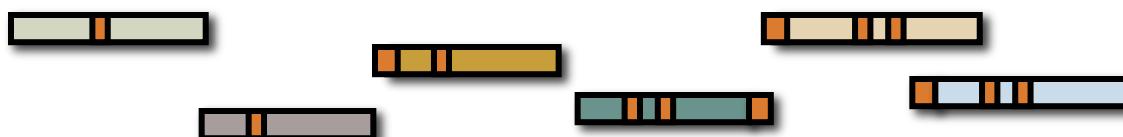
mRNAs  
combinatorial  
possibilities



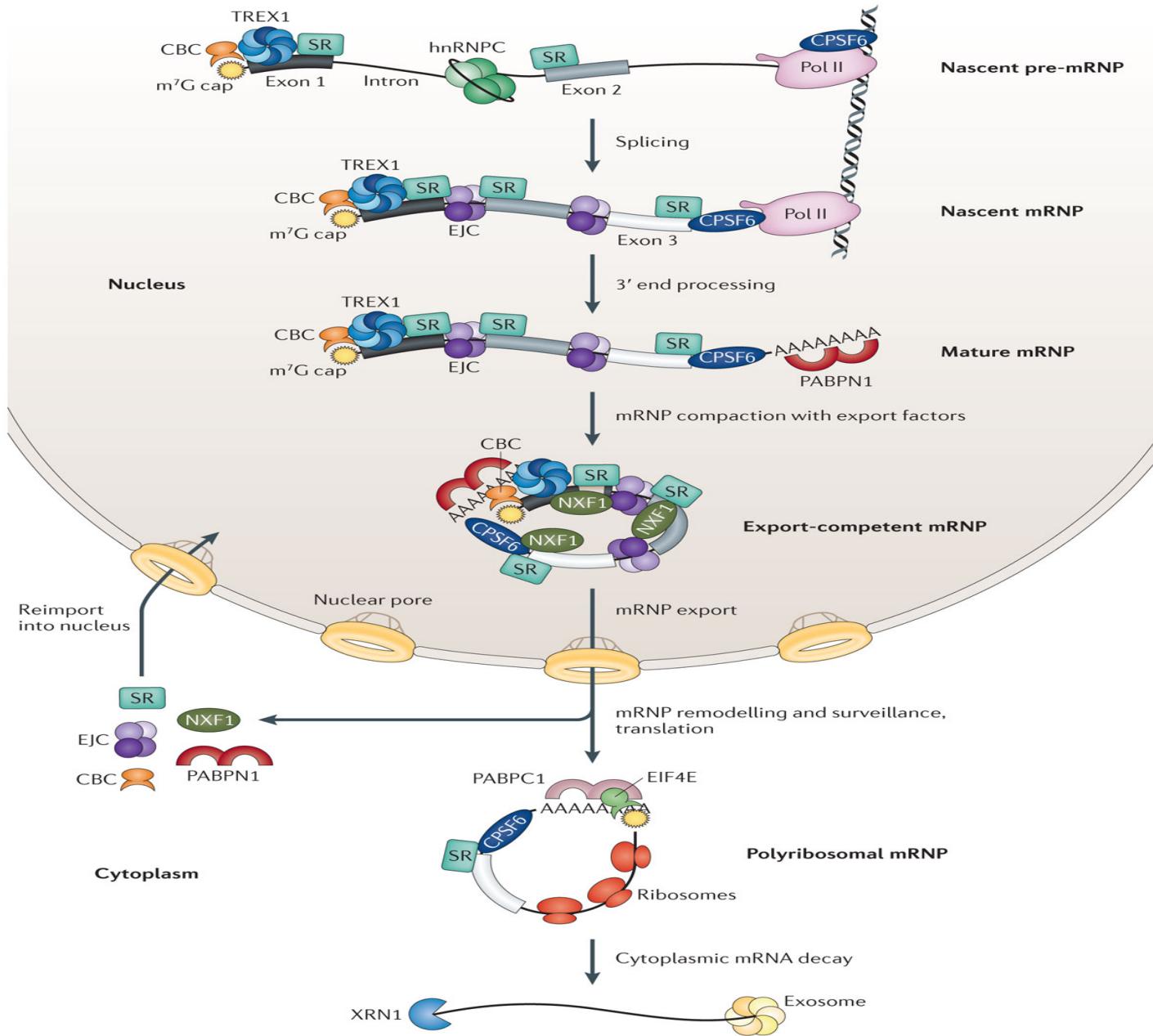
>90% of intron-containing genes are *alternatively spliced*

Tissue-specific regulation for >50% of splicing events

Proteins

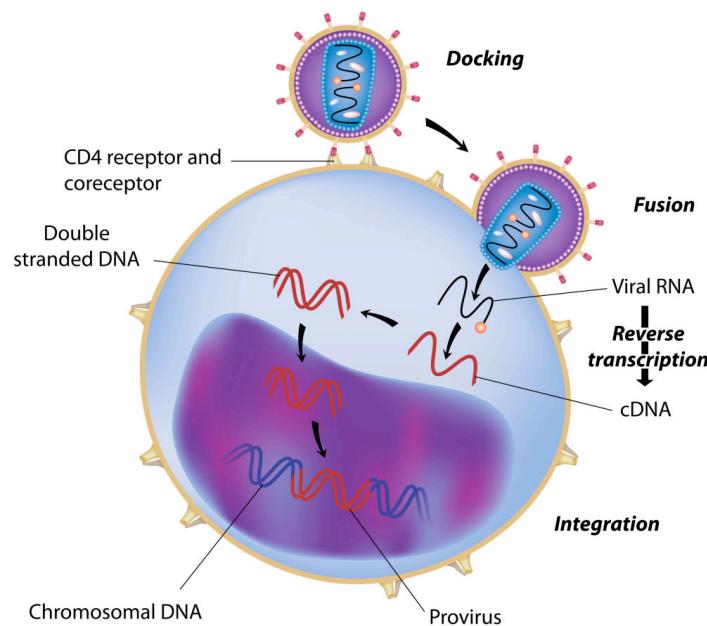


# How cells get the message: dynamic assembly and function of mRNA–protein complexes



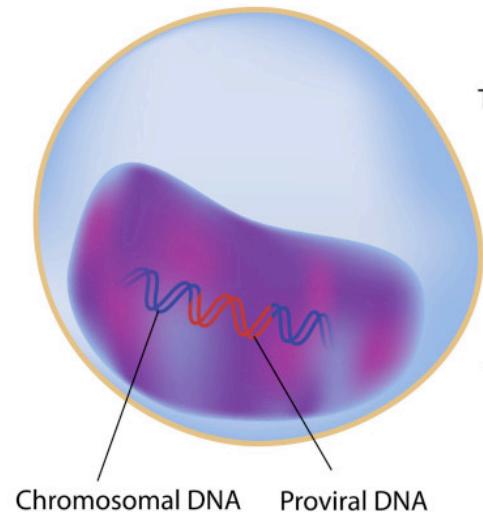
**RNA processing plays a large role in HIV  
replication**

## HIV Entry to T Cell

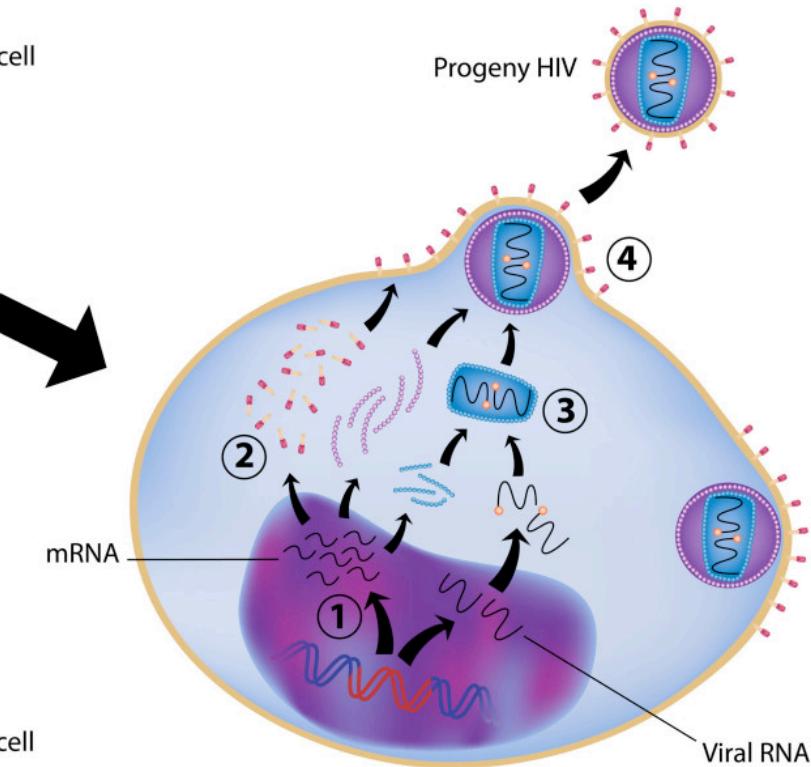


## HIV Infection in Target T cells

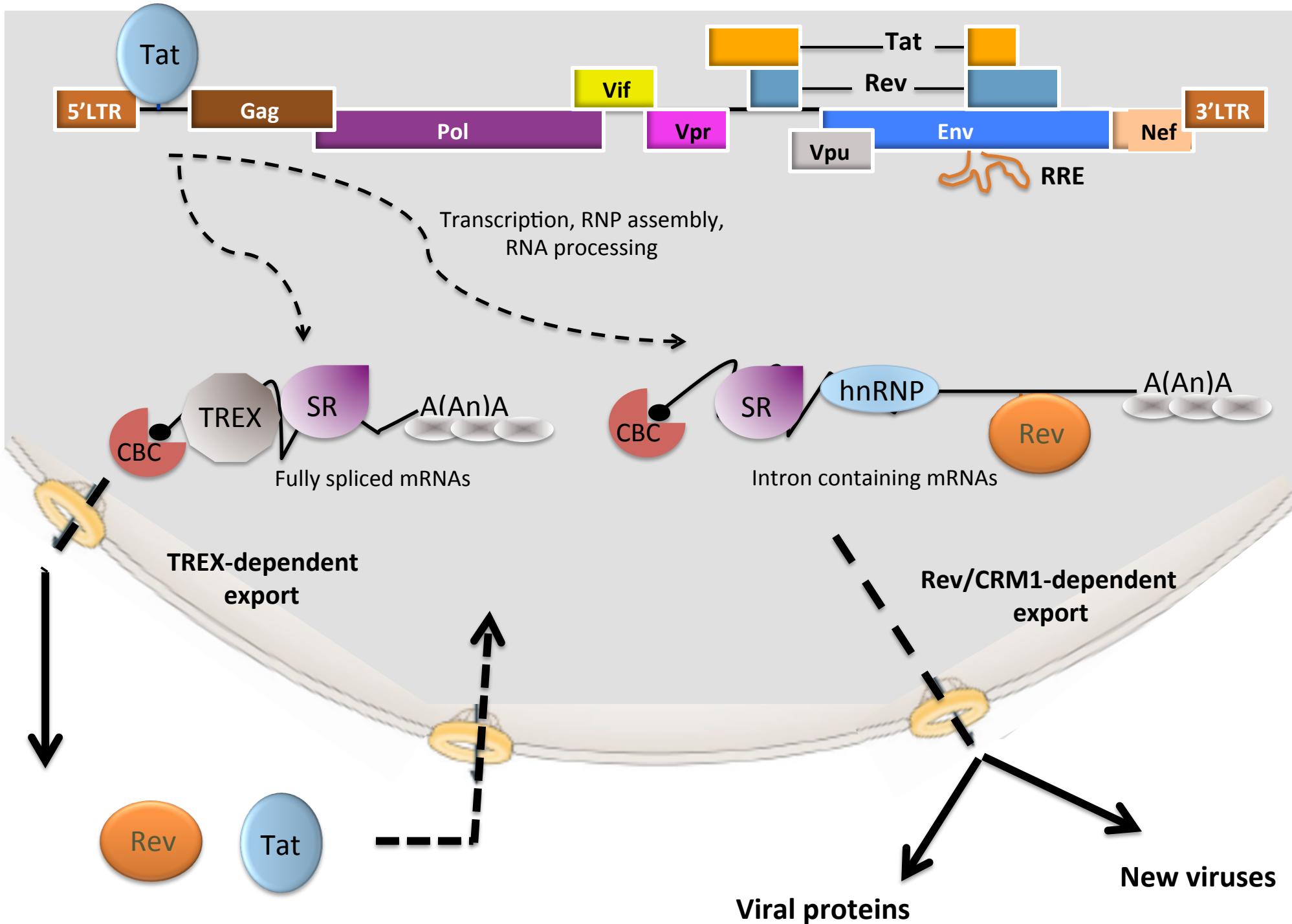
### Latent infection



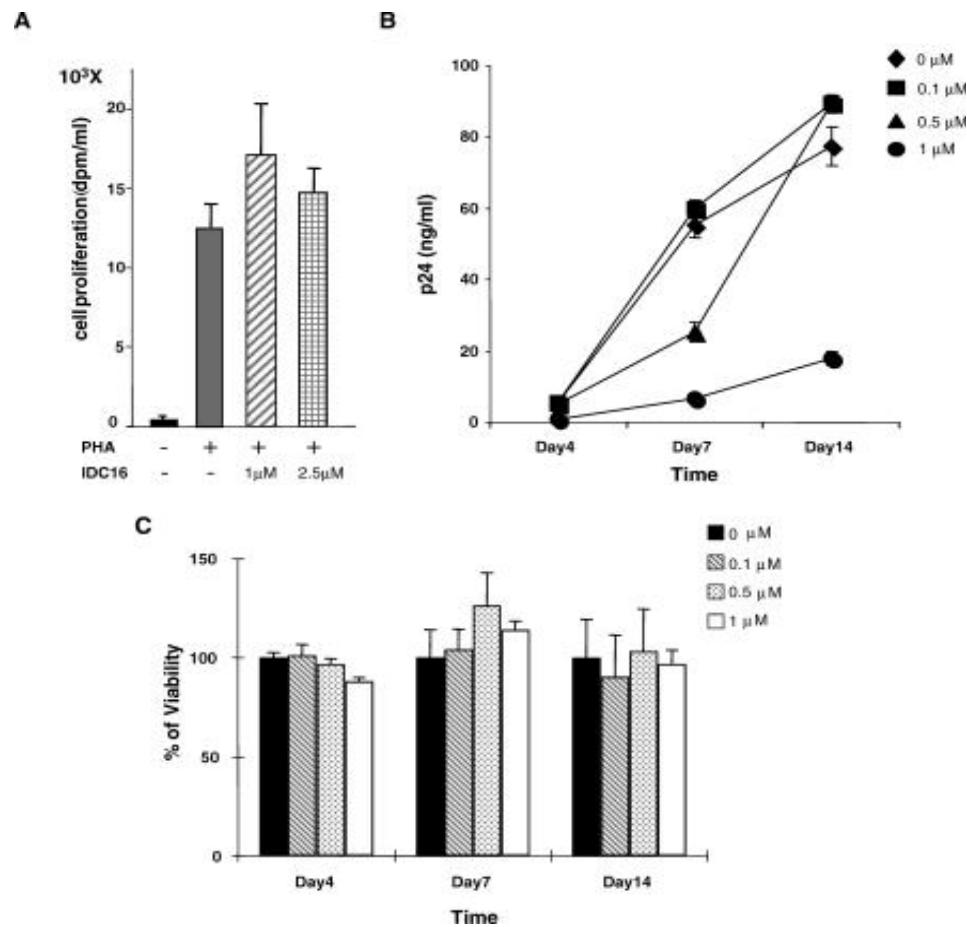
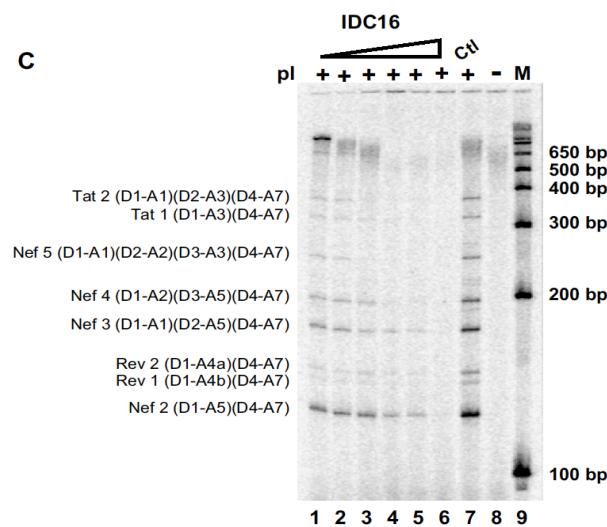
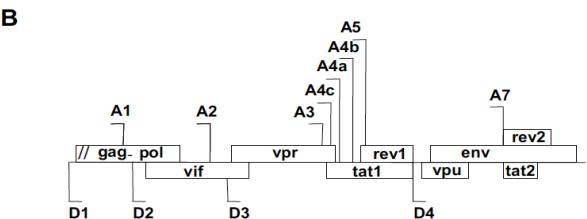
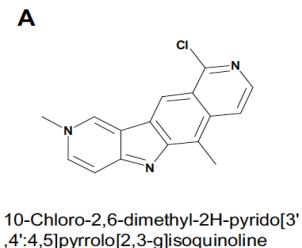
### Active infection



- ① Transcription of proviral DNA
- ② Synthesis of viral components
- ③ Assembly of viruses
- ④ Budding of viruses from the host cell



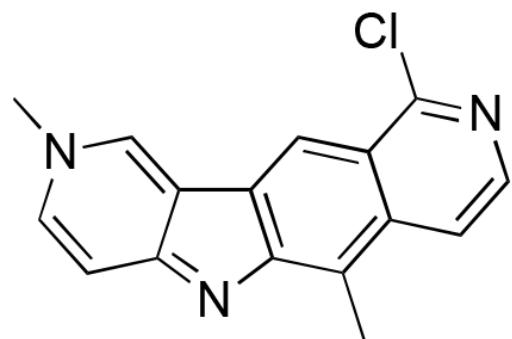
- Cellular quality control mechanisms retain and degrade unspliced or partially spliced mRNA
- The cellular quality control involves TREX and the Cap Binding Complex that facilitates Nuclear Export of both cellular and fully spliced viral RNA
- Rev protein allows the unspliced viral RNAs to escape the cellular quality control and to be exported by a mechanism dependent on CRM1 and the Cap Binding Complex
- Given that Rev protein is produced from fully spliced RNA, either inhibition or activation of viral RNA splicing will impede viral replication in infected cells



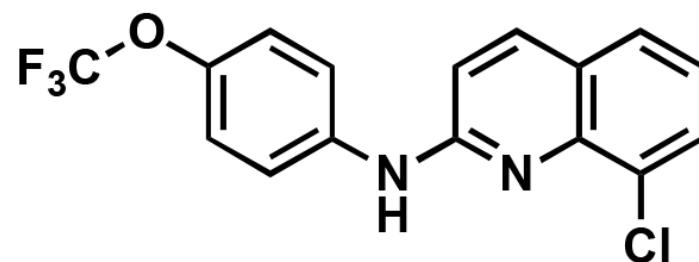
## Small-Molecule Inhibition of HIV pre-mRNA Splicing as a Novel Antiretroviral Therapy to Overcome Drug Resistance

Bakkour et al, PLoS Path, 2007

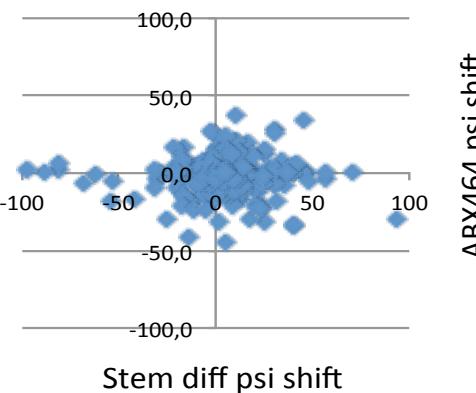
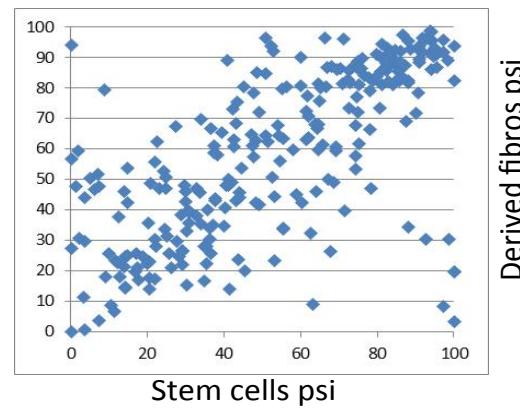
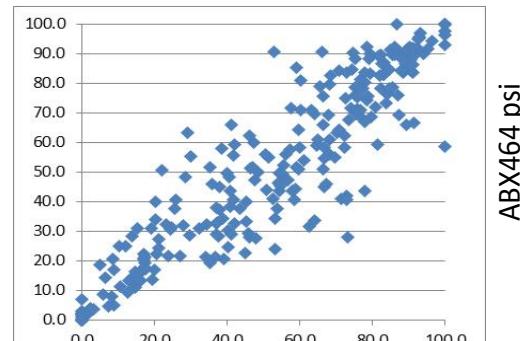
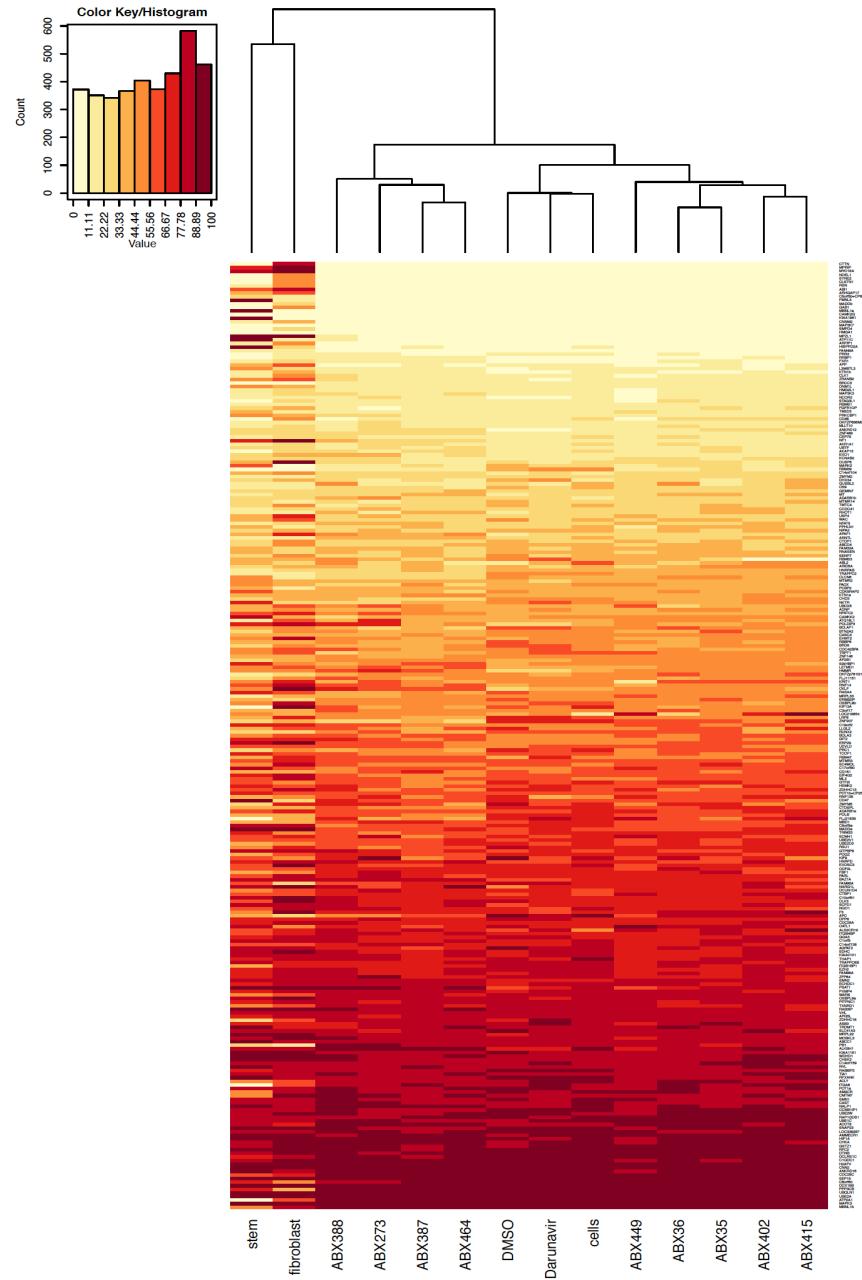
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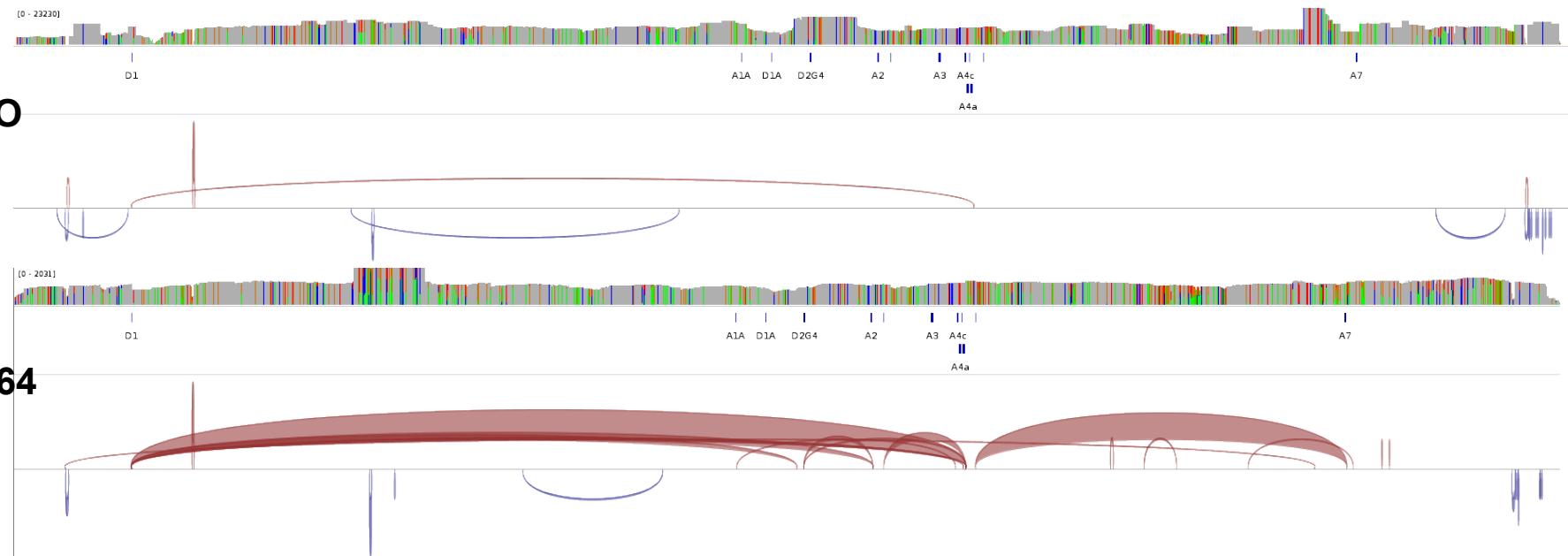
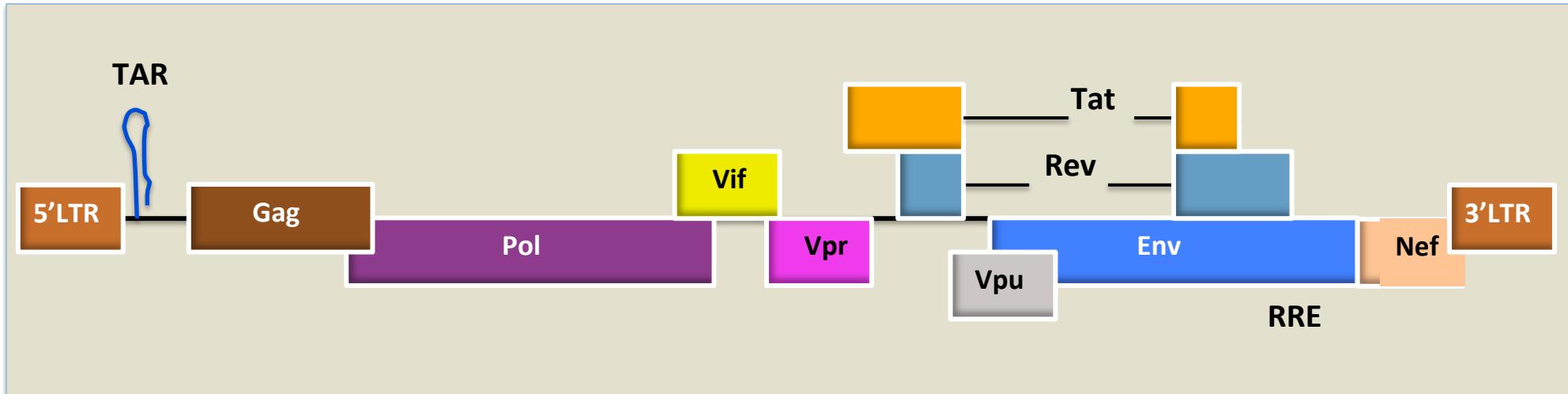


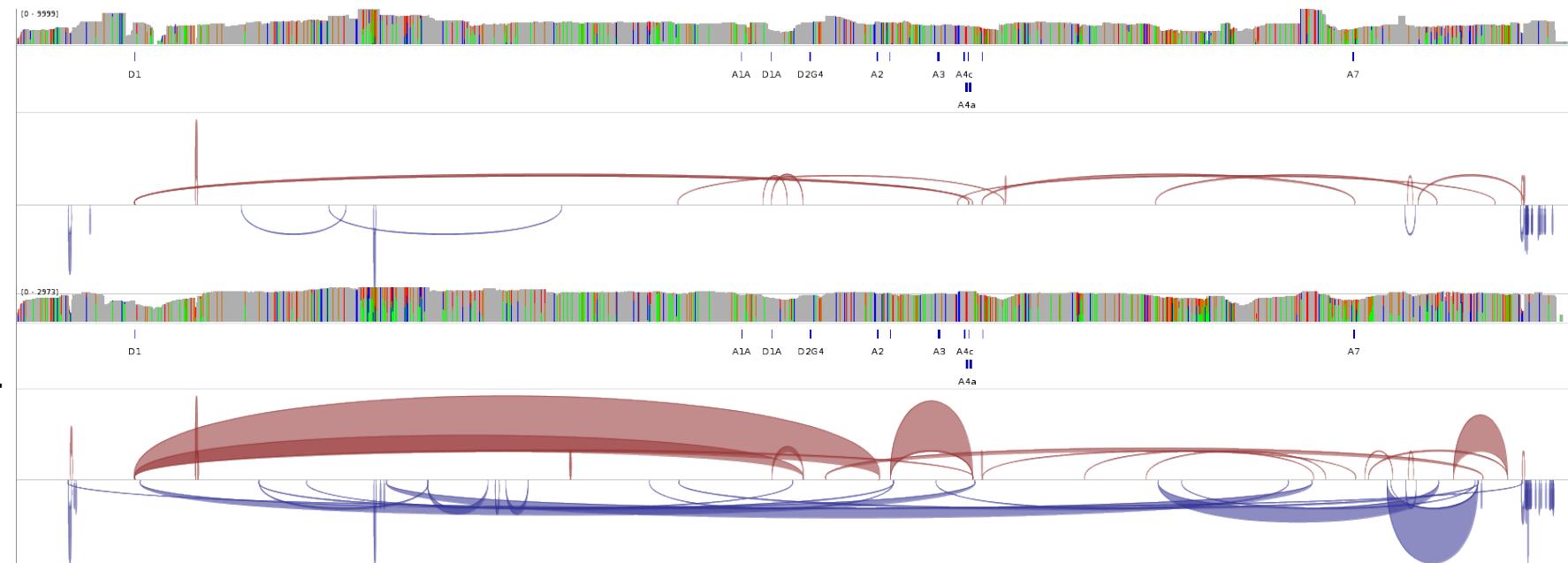
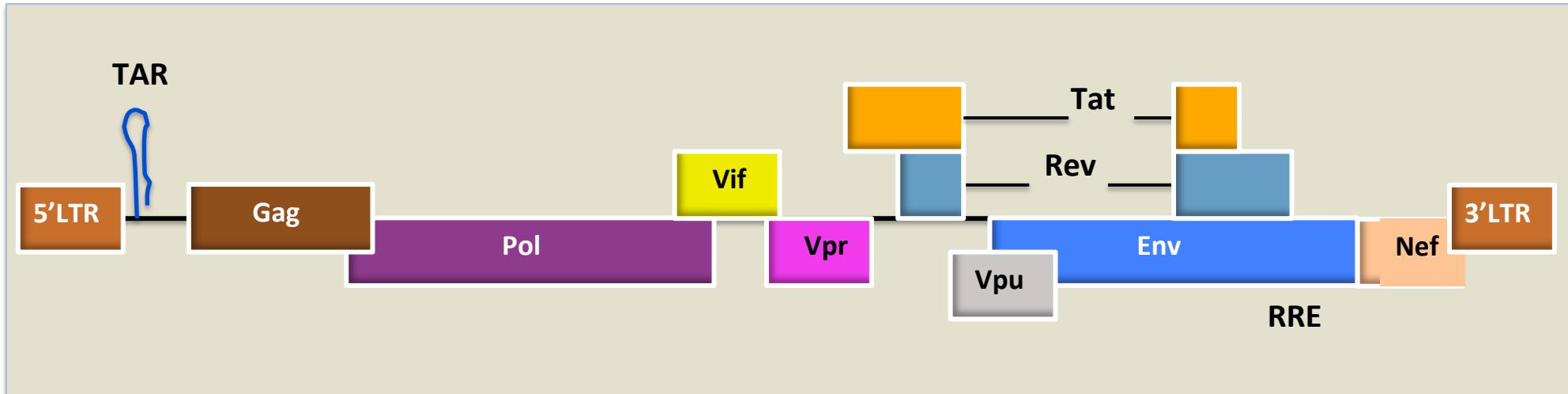
ABX464



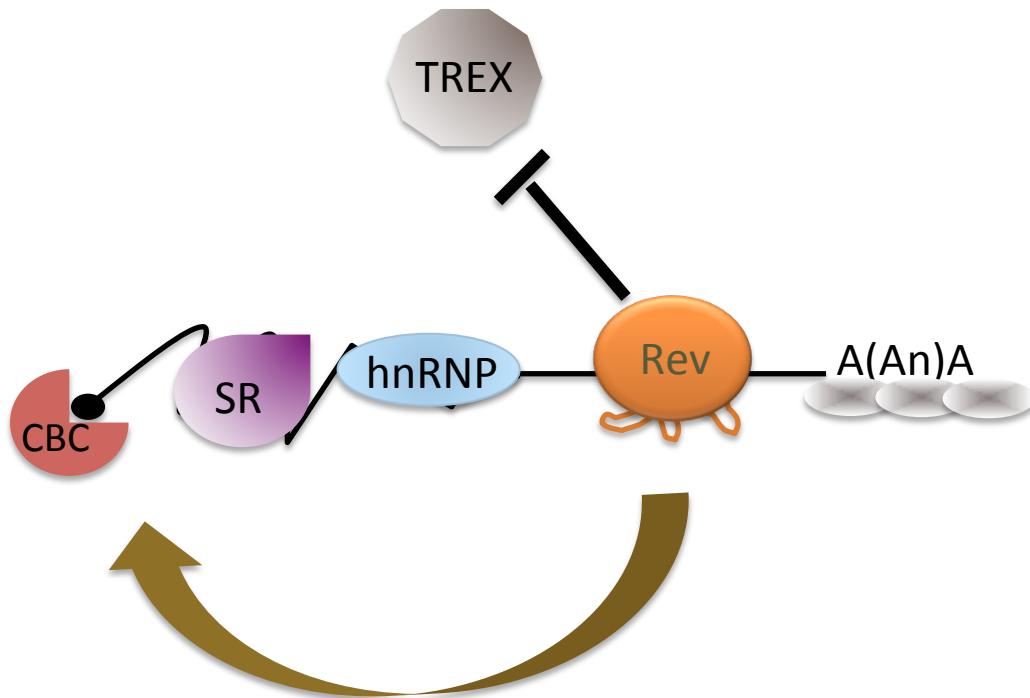
# cellular splicing is unaffected by the ABX464

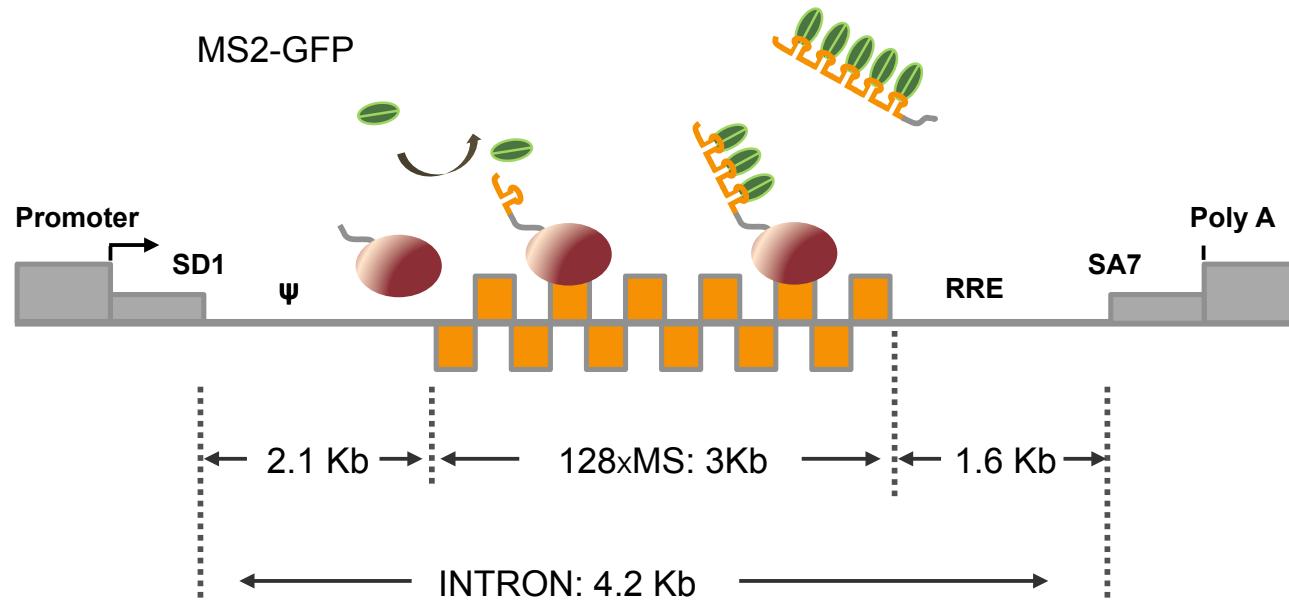




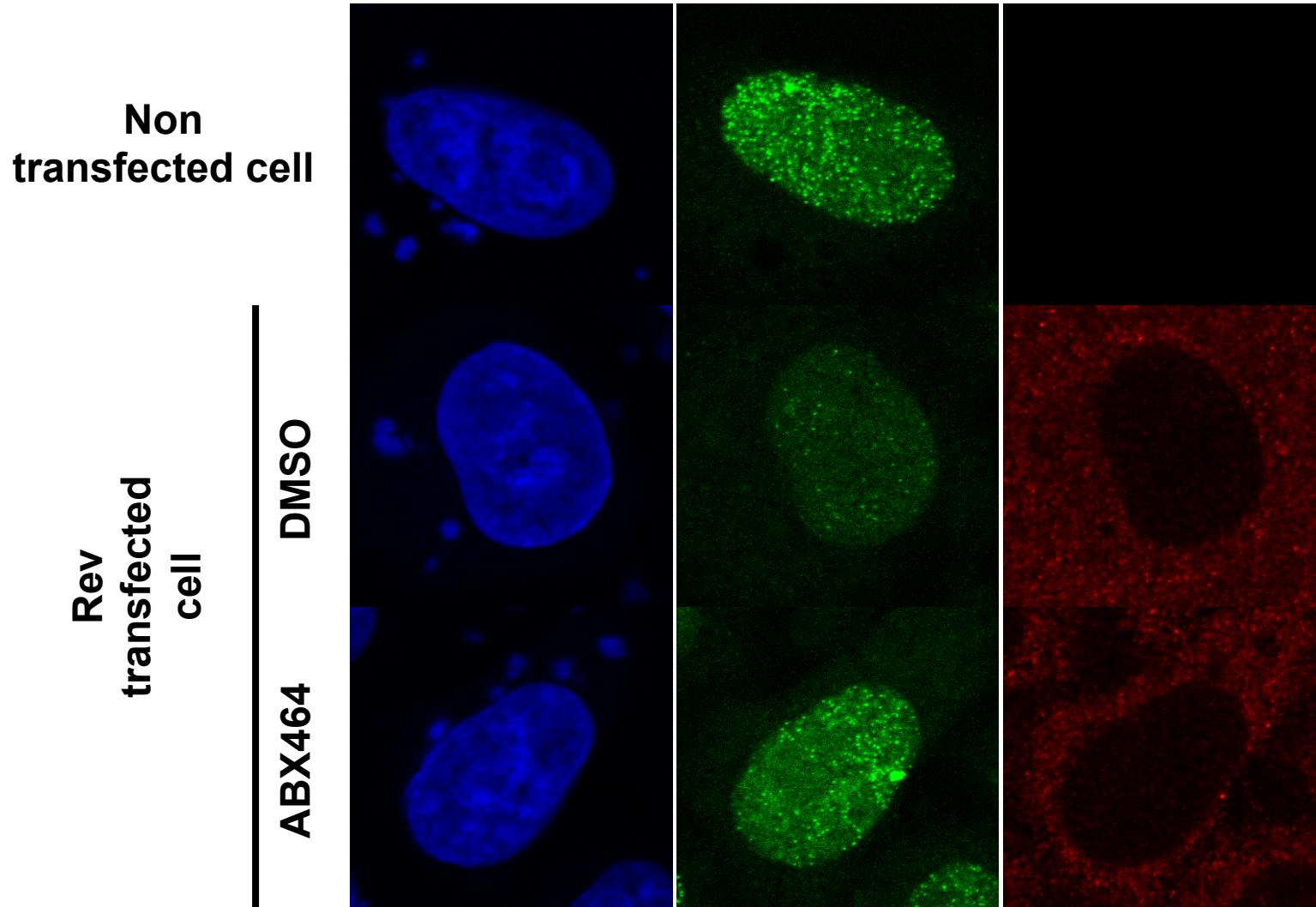


**Rev protein specifies the viral RNA export pathway through interaction with the Cap Binding complex**

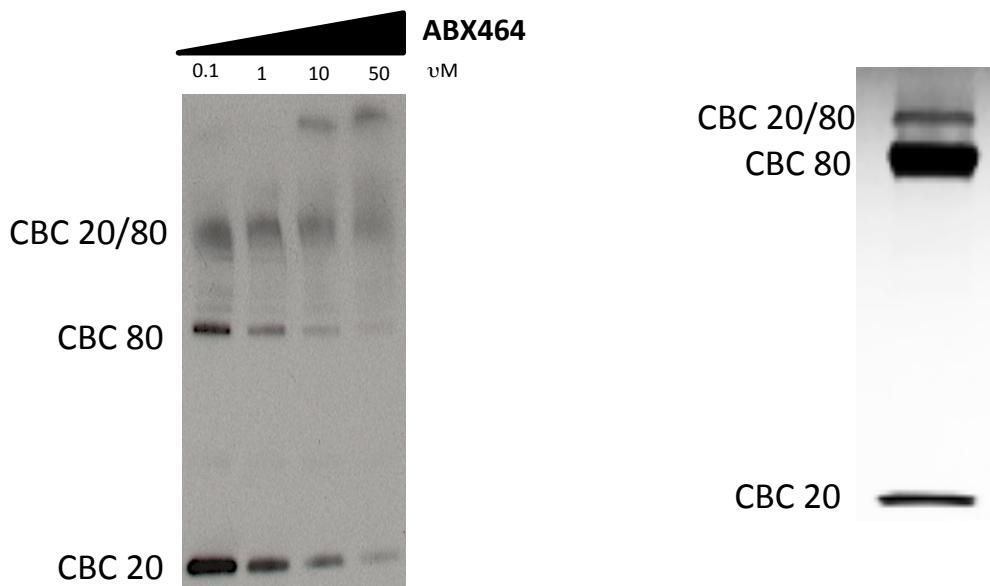


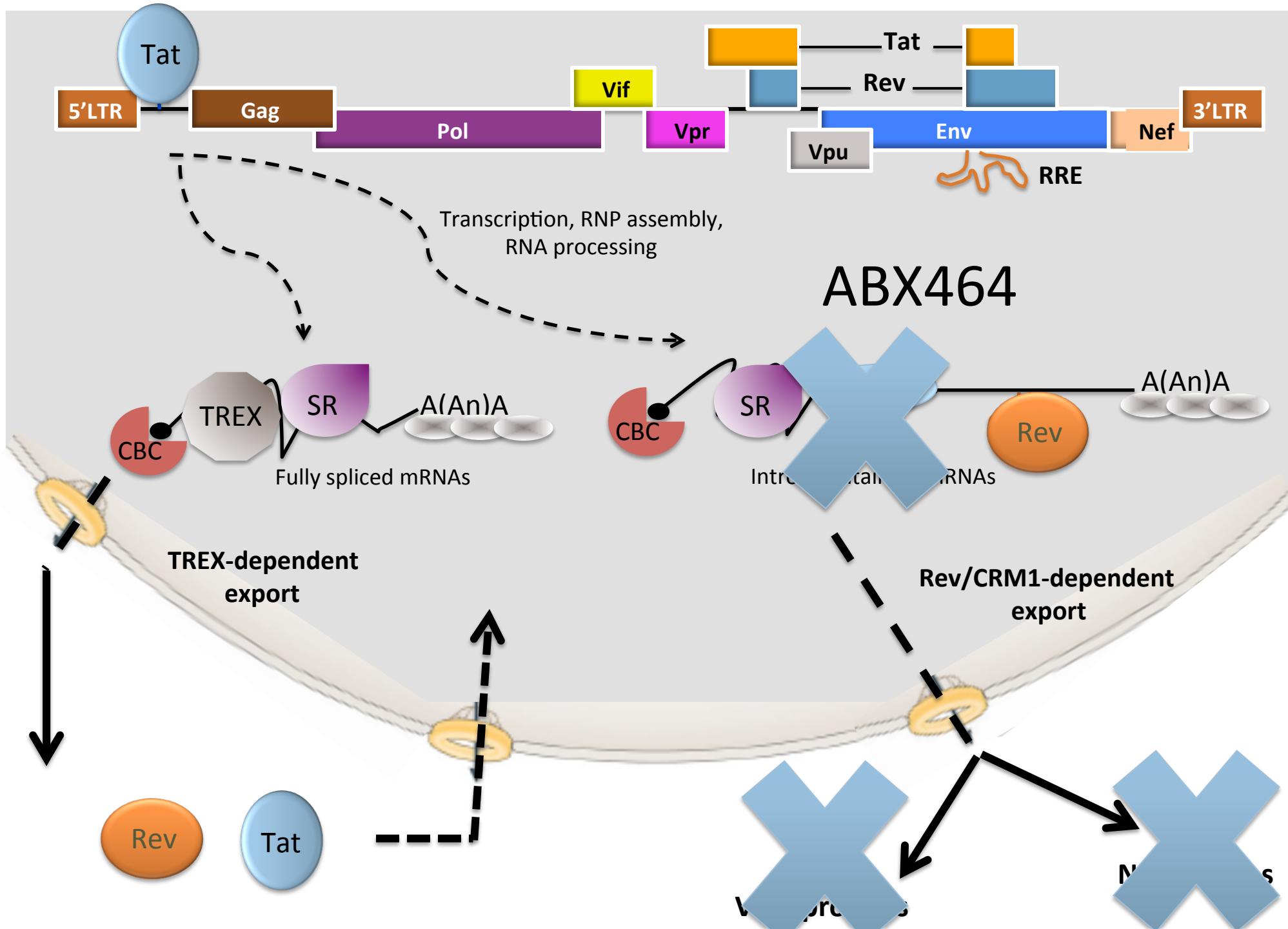


# ABX464 prevents Rev-mediated export of unspliced viral RNA

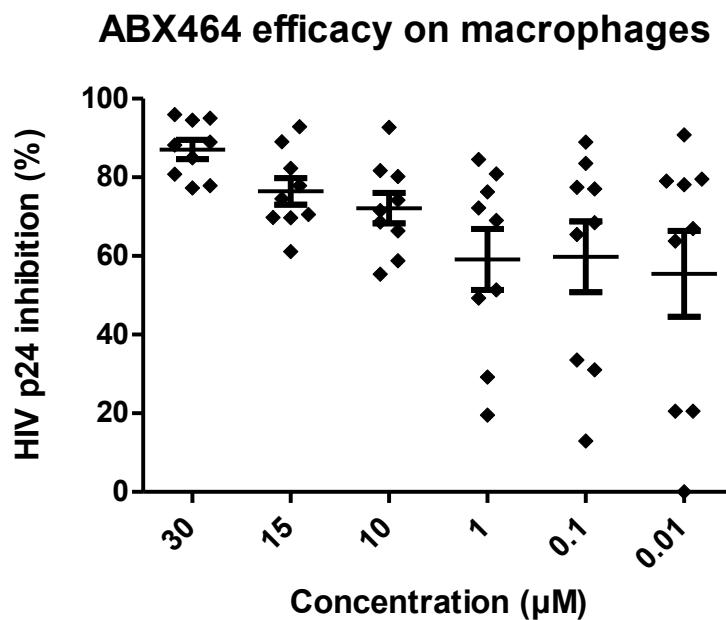
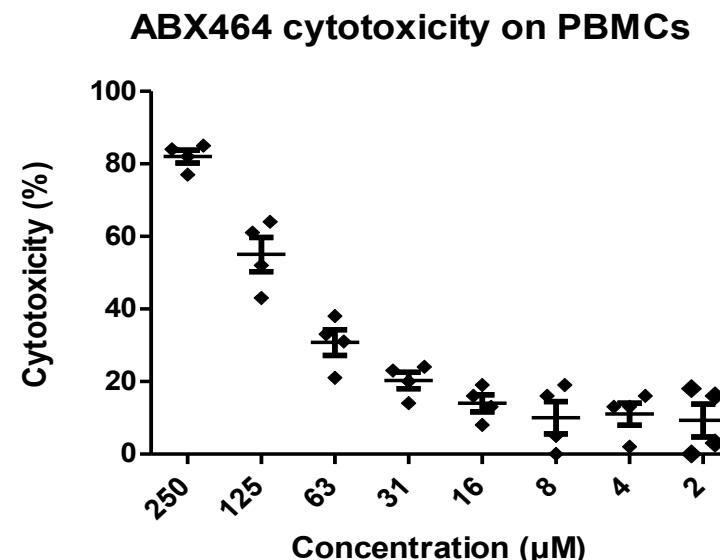
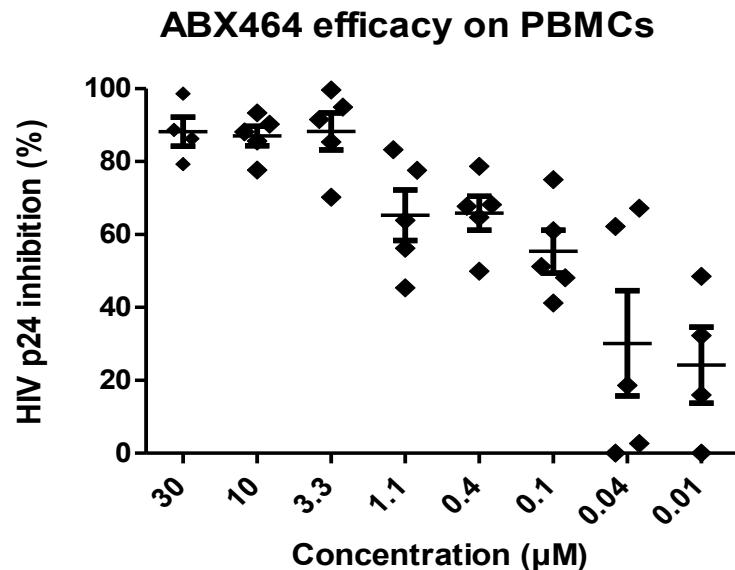


# ABX464 interacts with the Cap Binding Complex





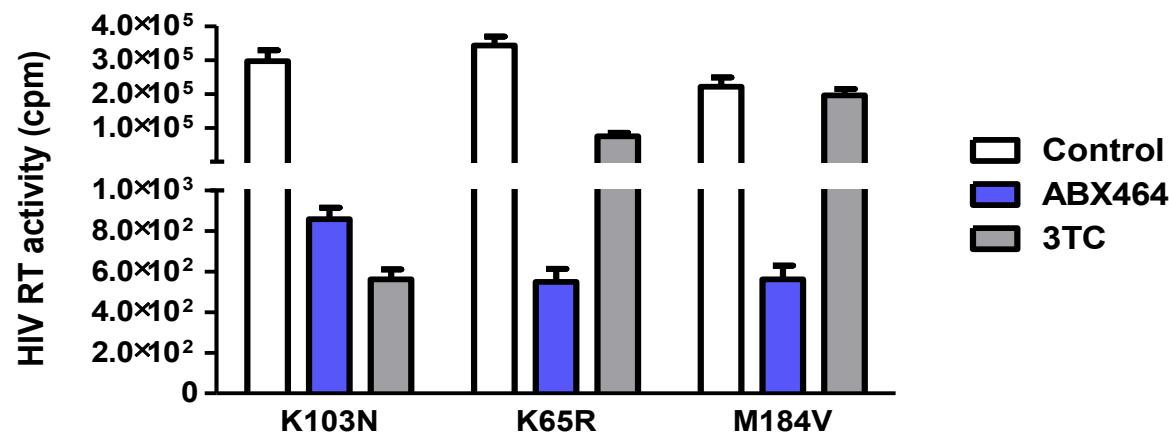
# Efficient inhibition of various HIV subtypes in PBMCs and macrophages by ABX464

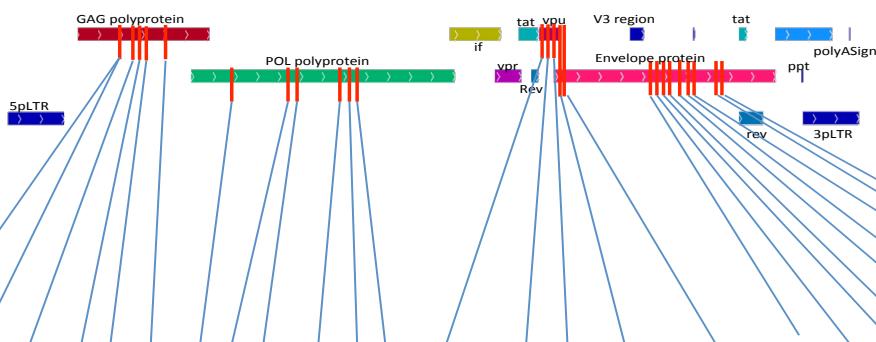
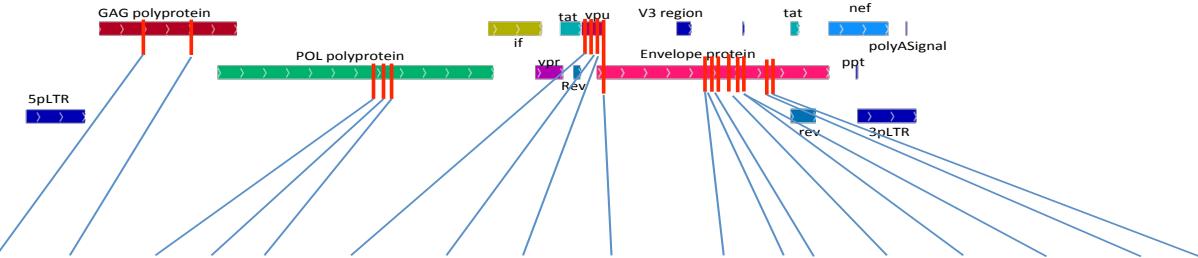


		% of inhibition with ABX464
HIV-1 strains		
HIV-1 B subtype	Ad8	71 $\pm$ 4
	AdaM	99 $\pm$ 1
HIV-1 C subtype	Isolate B	83 $\pm$ 8
	Isolate C	89 $\pm$ 1
HIV-1 recombinants	CRF01	82 $\pm$ 11
	CRF02	86 $\pm$ 3
	CRF06	80 $\pm$ 5

# ABX464 inhibits 3TC resistant strains

## Efficacy on NL4.3 resistant viruses

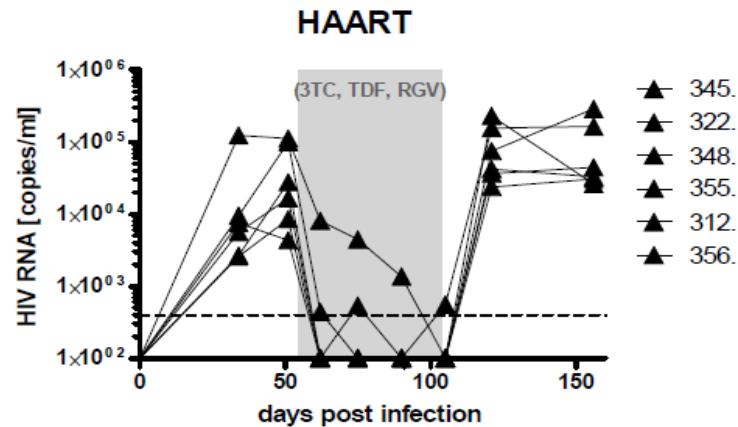
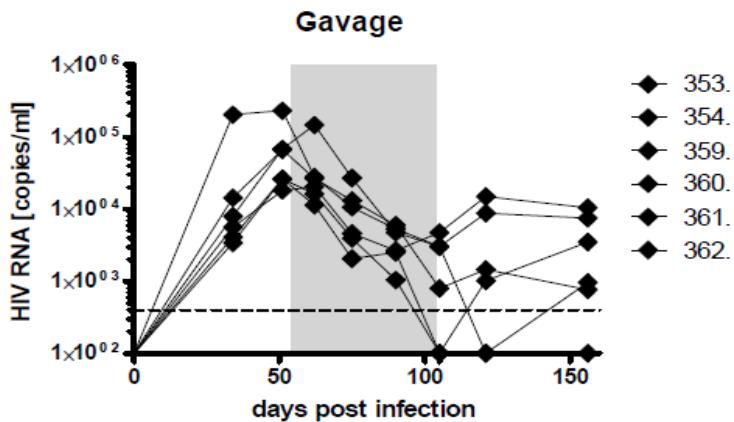
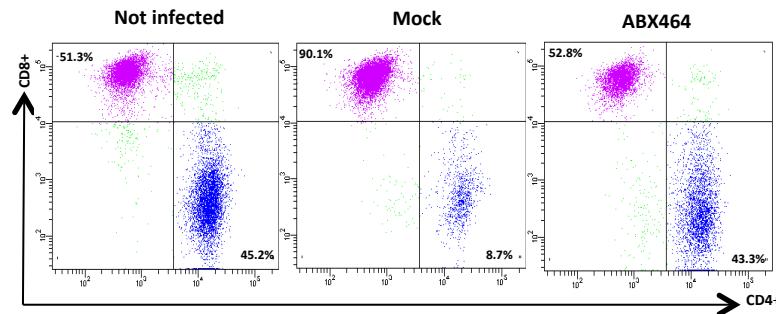
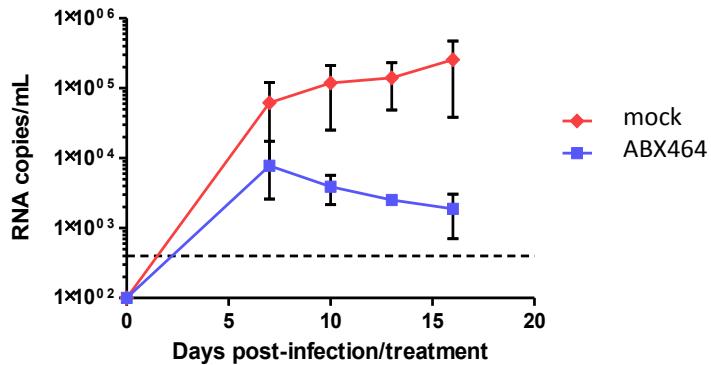




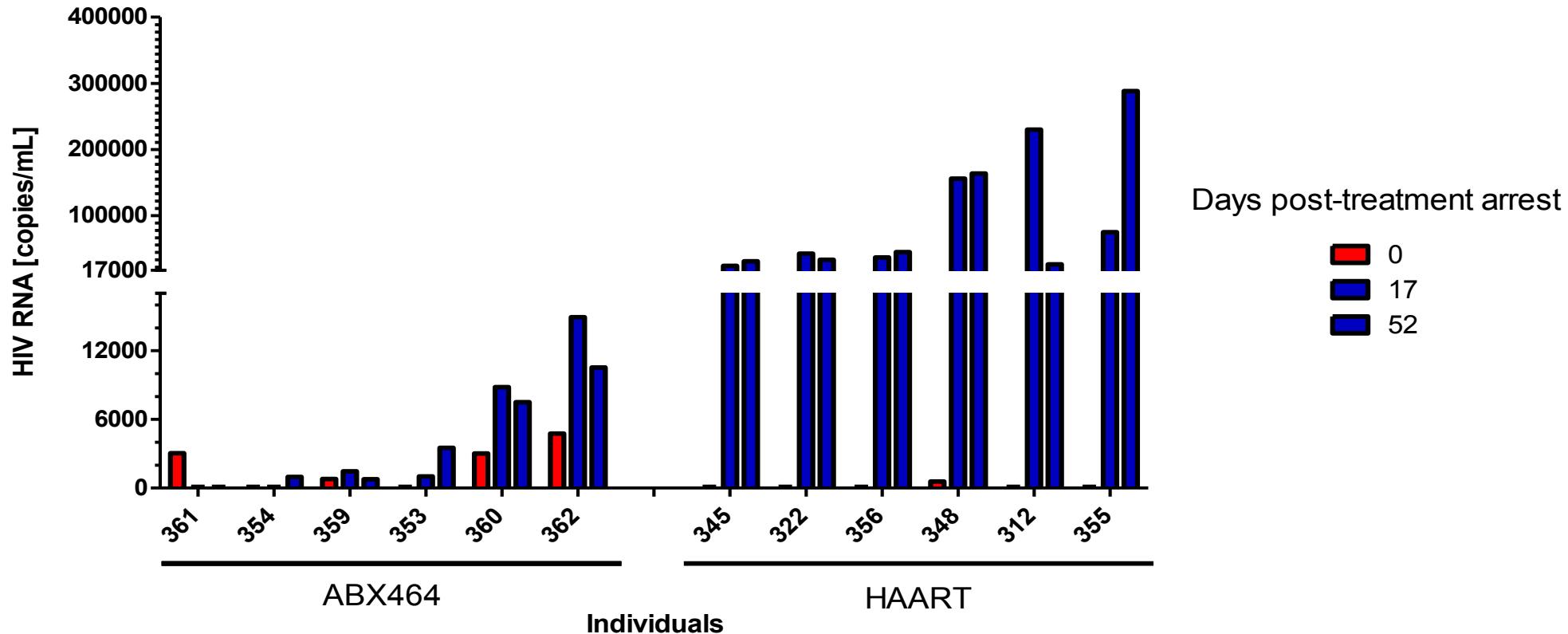
## HIV drug resistance *in vitro*\* (6-month follow-up)

Drug	Time to HIV resistance (weeks)	HIV Mutants
3TC	4	M184I/V
Tenofovir	12	K65R
Nevirapine	3	K103N, Y181C
Efavirenz	5	K103N, Y181C
ABX464	No HIV resistance	-

# Efficacy of ABX464 in humanized mouse models



# ABX464 is an anti-HIV drug able to suppress viral load sustainably after treatment arrest



## **ABX464 represents a novel class of anti-HIV molecules with unique properties.**

- ABX464 interferes with Rev-mediated RNA biogenesis
- ABX464 does not select for HIV specific mutations and it is not genotoxic
- ABX464 has a long lasting effect in humanized mice

- **Phase I data showed excellent safety and PK profile**

Paved the way for on-going phase IIa

- **Phase IIa dose ranging study initiated:**

80 naïve HIV patients

10 groups of 8 patients Escalating Doses: 25, 50, 75, 100 and 150 mg per day

# Acknowledgments



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## Acknowledgments

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