



Basic science of HIV Cure approaches

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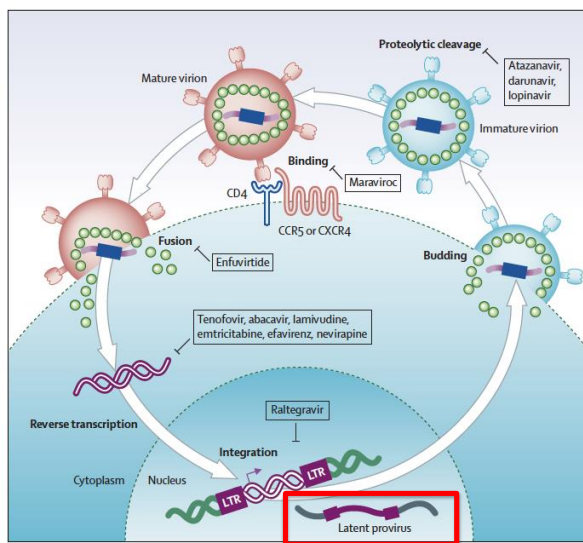
HIV-1 & treatment in 2017



- Worldwide ~37 million people infected with HIV-1
- Current treatment is **antiretroviral therapy (ART)**
- ART = combinations of anti-HIV drugs targeting multiple virus life cycle stages

UNAIDS 2016-Factsheet 2016. WHO 2016; Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection.

HIV life cycle & antiretroviral drug targets



**Latent HIV provirus =
major obstacle to an
HIV cure**

Volberding & Deeks *Lancet* 2010; 376:49-62

Why do we need an HIV cure?



- **ART** has revolutionised HIV therapy, but it has limitations
- WHO guidelines recommend all people living with HIV should be treated with ART
- **Access**; only ~18 million people have access to ART
- **ART is not a cure**; the latent provirus is not impacted by antiretroviral drugs

WHO 2016; Consolidated guidelines on the use of antiretroviral drugs for treatment and preventing HIV infection.

HIV cure strategies

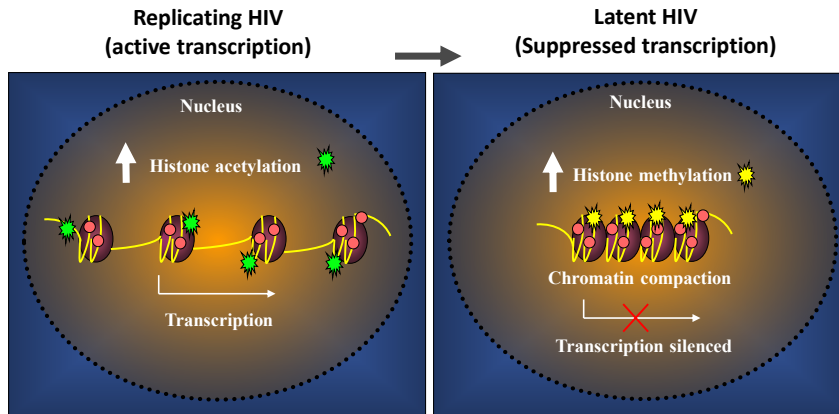


- Eradication or sterilising cure
 - kill infected cells or excise HIV DNA from infected cells
 - Patients may no longer require ART
- Functional cure
 - Gene therapy to deliver anti-HIV agents
 - Patients may no longer require ART

HIV latency mechanism



- Epigenetic gene silencing is essential for controlling gene expression



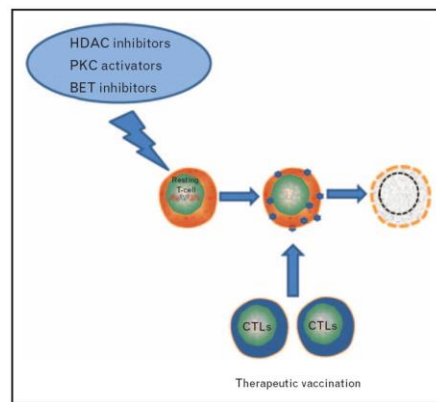
- Histone deacetylase (HDAC) enzyme removes acetylation groups on chromatin

Eradication approach



- Shock and Kill approach
- Single latency reversing agents (LRA) not effective
- Clinical trials underway with combination LRAs (virostat & ingenol)
- Combo treatment caused harmful brain inflammation in macaques

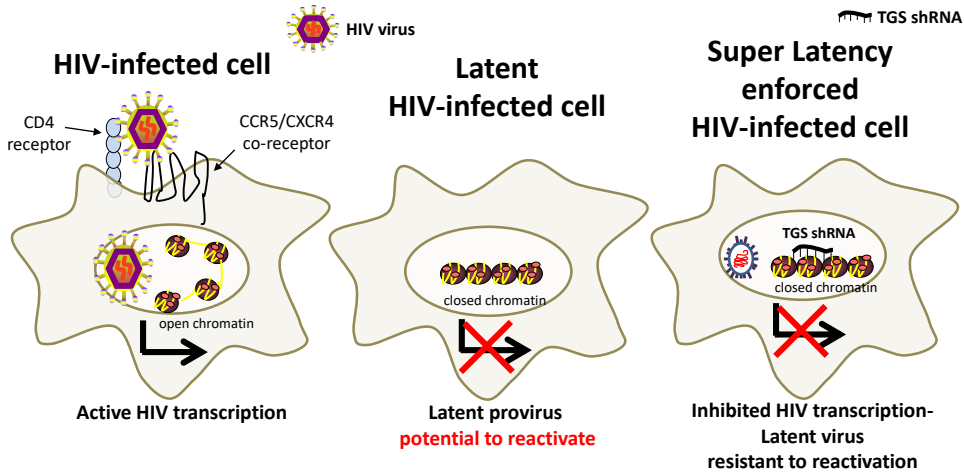
'Shock and kill' strategy for curing HIV may endanger patients' brains – ScienceNews Dec 2016




Archin & Margolis Curr Opin Infect Dis 2014; Gama et al., AIDS, 2017; 31 (1): 5

Functional cure approach  

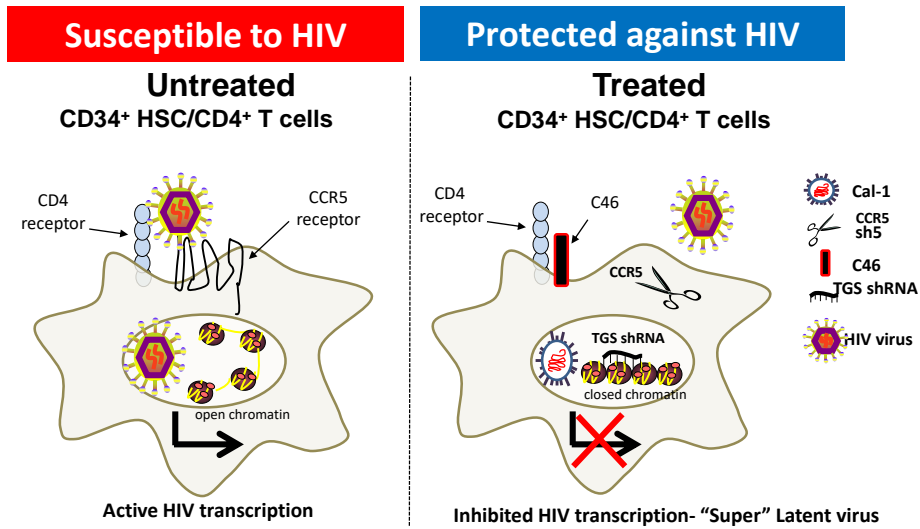
- HIV-1 provirus is locked in latency without ART



Suzuki et al., *J RNAi and Silencing* 2005; Yamagishi et al., *JBC* 2009; Suzuki et al., *RNA Biology* 2011; MTNA 2013; Ahlenstiel et al., *NAR* 2012; MTNA 2015.

HIV Functional cure strategy  

- HIV is unable to enter “protected” target cells



Calimmune Inc. Wolstein et al., 2015; Suzuki et al., *J RNAi and Silencing* 2005; Yamagishi et al., *JBC* 2009; Suzuki et al., *RNA Biology* 2011; MTNA 2013; Ahlenstiel et al., *NAR* 2012; MTNA 2015.

Summary



- An HIV cure is necessary to control the HIV latent reservoir
 - Two approaches to cure strategies include;
 - Eradication / sterilising cure
 - Functional cure
 - All approaches aim to control HIV reservoir
 - Ultimately with the patients no longer requiring ART
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