AETC AIDS Education & Training Center Program Southeast

Antiretrovirals

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Faculty Disclosure

- None

Educational Need/Practice Gap

Gap

New antiretroviral agents intended for the management of HIV infection continue to be introduced. These agents may represent drugs with unique mechanisms of action.

Need

Practitioners must stay abreast of the latest antiretroviral medications that have been approved and/or that may soon be approved.

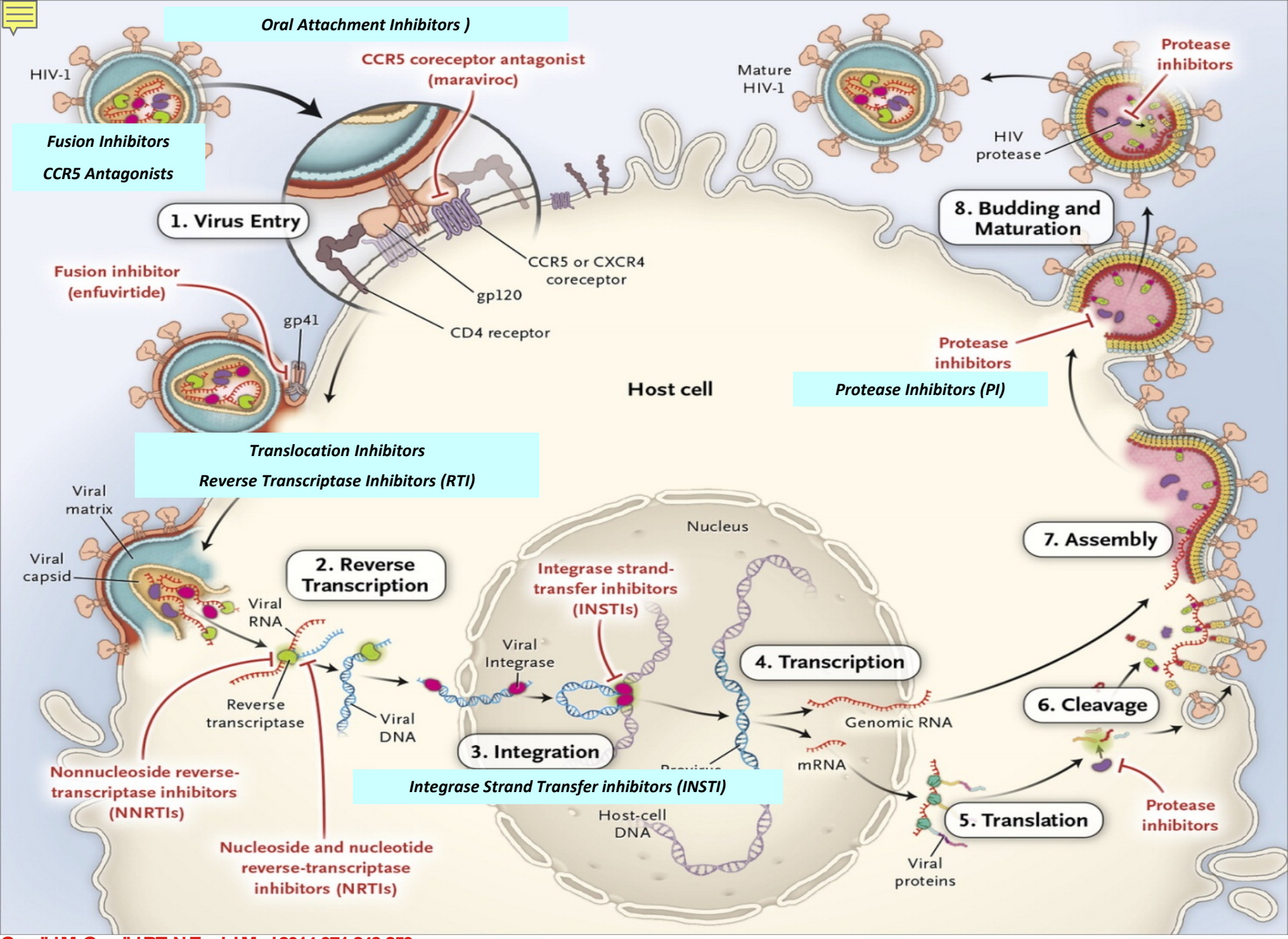
Objectives

Upon completion of this educational activity, you will be able to:

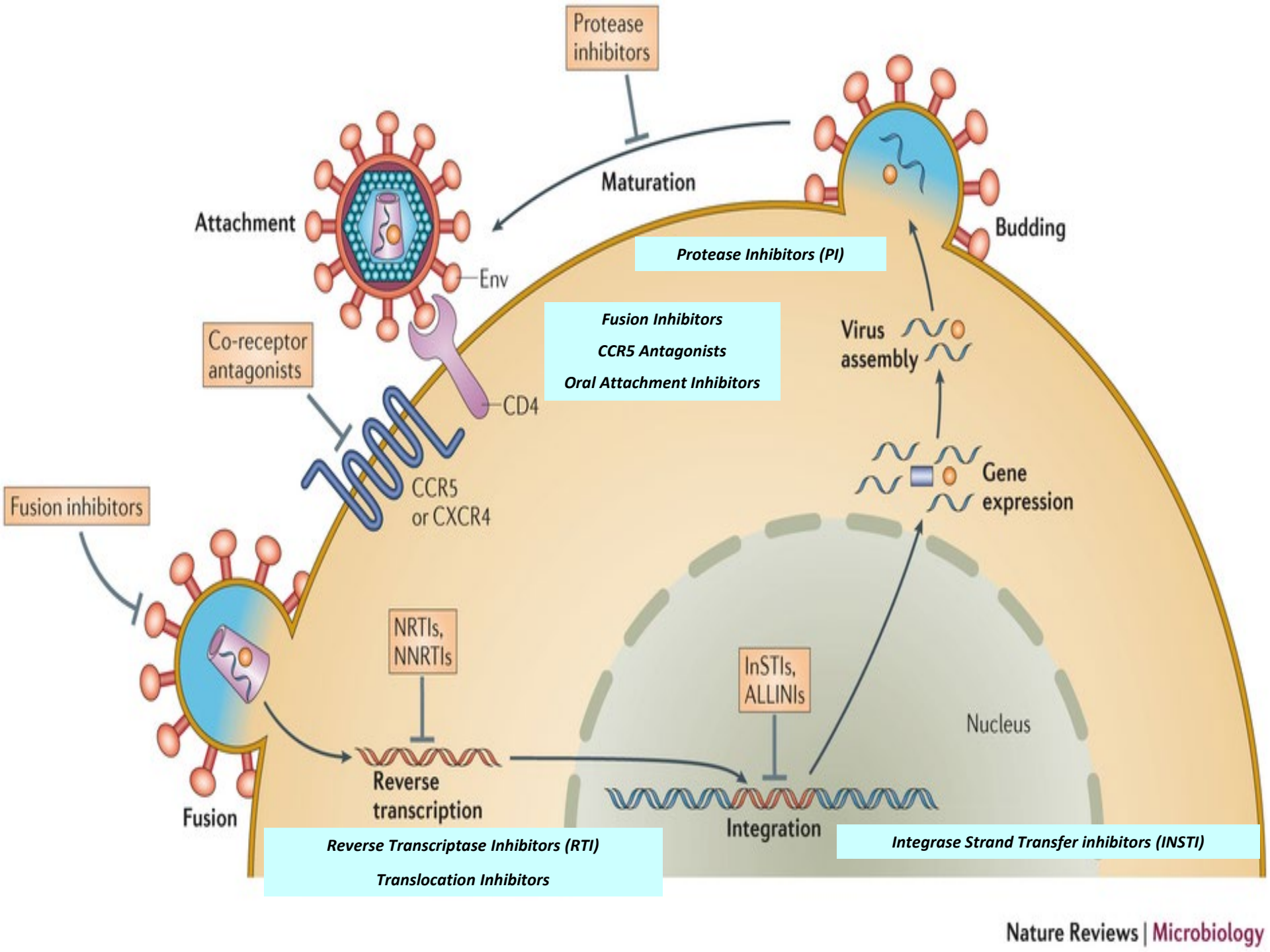
- Describe the mechanism of action and common clinical aspects of new antiretroviral medications.
- Discuss antiretroviral medications currently under study.

Expected Outcome

- To be able to properly prescribe and monitor various antiretrovirals in the management of HIV infection.

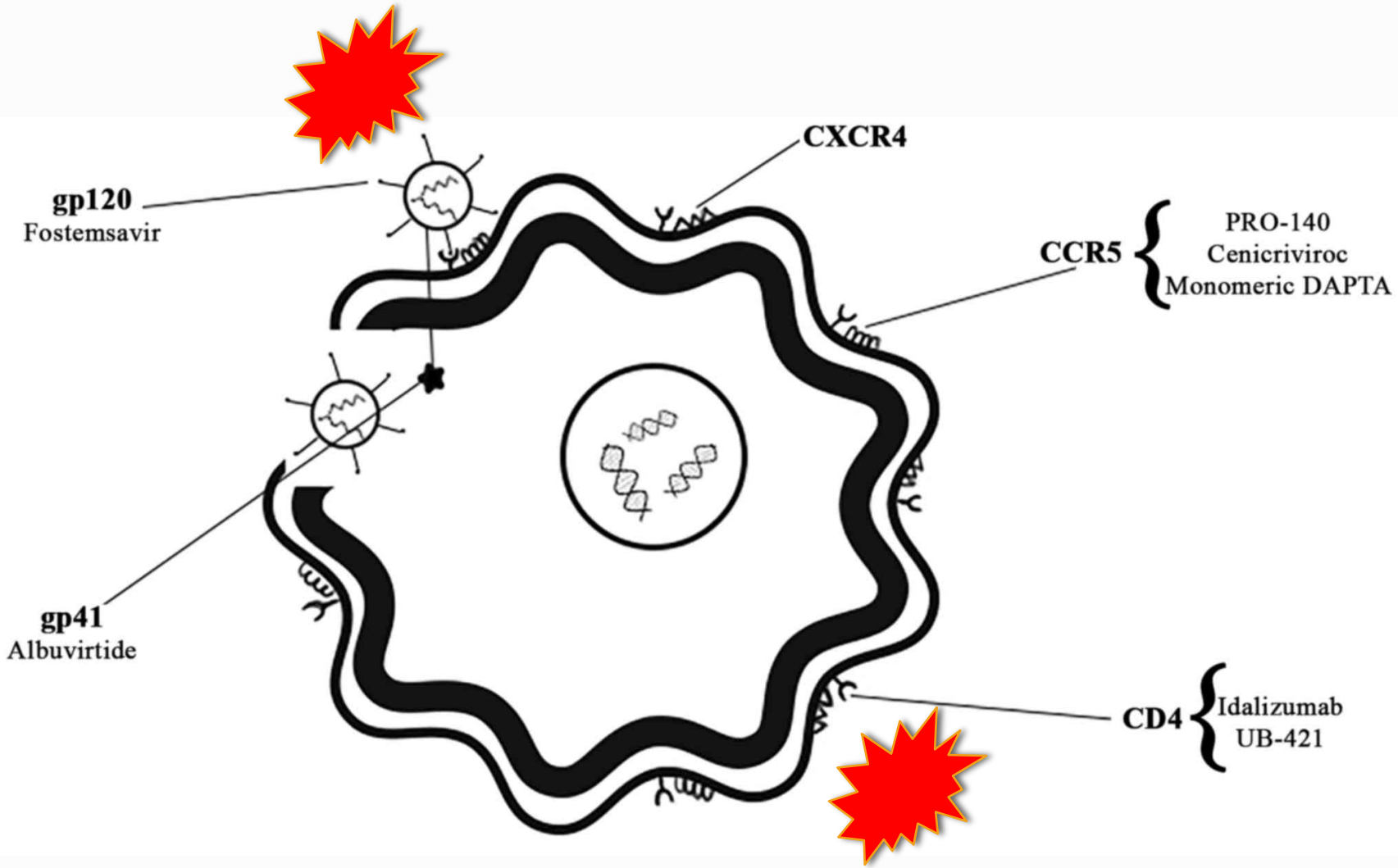


Gandhi M, Gandhi RT. N Engl J Med 2014;371:248-259.



Nature Reviews | Microbiology

CD4+ versus Viral Connectivity



https://www.spandidos-publications.com/10.3892/mmr.2019.9840

*Red – combination agents

Antiretroviral Therapy

Nucleoside and Nucleotide RTIs (NRTI)

- Zidovudine, AZT
- Abacavir, ABC
- Lamivudine, 3TC
- ~~Didanosine, ddI~~
- ~~Stavudine, d4T~~
- Tenofovir, TDF
- Tenofovir, TAF
- Emtricitabine, FTC
- AZT/3TC
- AZT/3TC/ABC
- ABC/3TC
- TDF/FTC
- TAF/FTC

Non-nucleosides (NNRTI)

- ~~Delavirdine, DLV~~
- ~~Nevirapine, NVP~~
- Efavirenz, EFV
- Etravirine
- Rilpivirine
- Doravirine

Fusion Inhibitors

- Enfuvirtide, ENF or T20

Entry Inhibitors

- Ibalizumab (IV)

Attachment Inhibitors

- Fostemsavir (PO)

CCR5 Receptor Blocker

- Maraviroc

Protease Inhibitors (PIs)

- ~~Indinavir, IDV~~
- ~~Saquinavir, SQV~~
- ~~Nelfinavir, NFV~~
- Atazanavir, ATV
- ~~Fosamprenavir, FPV~~
- Lopinavir/ritonavir
- Tipranavir
- Darunavir
- Darunavir/cobicistat
- Atazanavir/cobicistat

Integrase Inhibitors (INSTI)

- Raltegravir, RAL
- Elvitegravir, EVG
- Dolutegravir, DTG

Single Tablet Regimens/Fixed Dose Combinations

- FTC/TDF/EFV (Atripla®)
- FTC/TDF/RPV (Complera®)
- FTC/TAF/RPV (Odefsey®)
- 3TC/TDF/EFV (Symfi®)
- FTC/TDF/EVG/cobi (Stribild®)
- FTC/TAF/EVG/cobi (Genvoya®)
- ABC/3TC/DTG (Triumeq®)
- FTC/TAF/DAR/cobi (Symtuza®)
- FTC/TAF/BIC (Biktarvy®)
- DOR/TDF/3TC (Delstrigo®)

**DTG/RPV (Juluca®) *DTG/3TC (Dovato®)*

Do we need more ARVs?

- More FDCs?
- More of the same? NRTIs, NNRTIs, PIs, INSTIs, etc.
- Unique targets?
- Safer agents?
- Fewer dug interactions?
- Higher resistance ceilings?
- Long-acting agents?

Resistance

- 84,611 de-identified samples from pts in the US from 2012-2018
- 33% had reduced susceptibility to at least one ARV
- Decreasing prevalence of multiclass ARV resistance corresponding to availability of newer, more effective drugs and formulations with favorable cross resistance profiles

ARV	2012	2018
NRTIs	55%	41%
NNRTIs	76%	73%
PIs	15%	8%
INSTIs	20%	17%
Multi-Class	3%	1%

Heneger CE et al. CROI 2020; Abstr. 521

A New Antiretroviral (Approved)

FOSTEMSAVIR

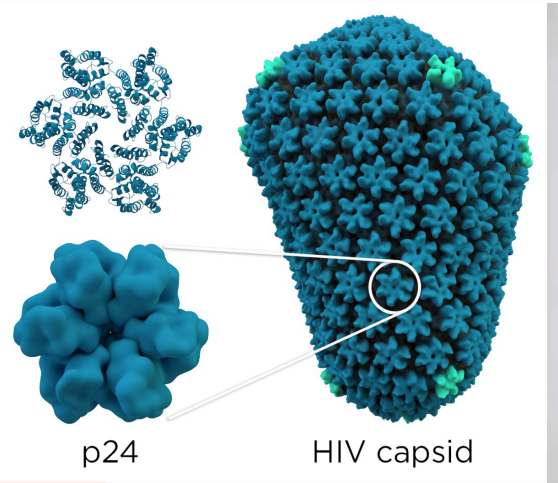
- Oral attachment inhibitor
- Small molecule agent that binds **viral** gp120
- Salvage therapy: resistance, intolerance, safety

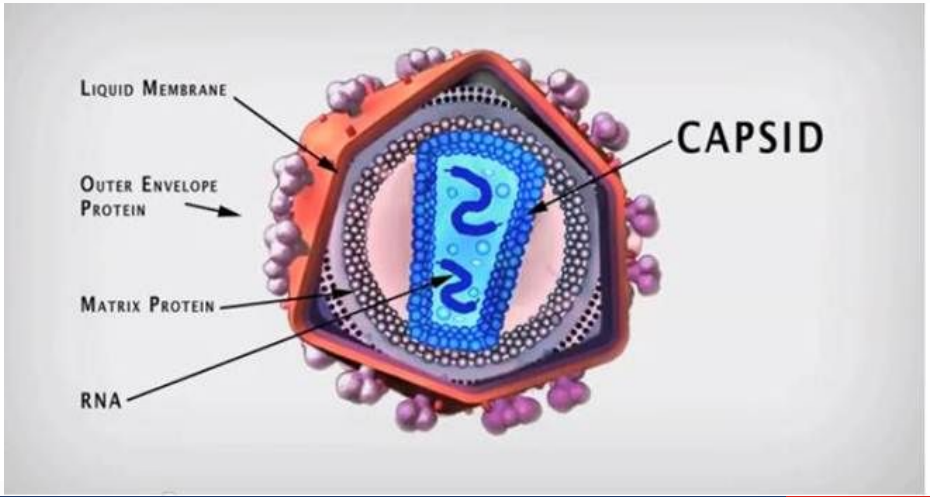
- Fostemsavir (Rukobia®)
- Prodrug of temsavir
- Active against R5, X4 and mixed trophic species
- N/V
- Interaction – ethinyl estradiol ()
- 600 mg XR tabs 1 PO BID

Agents in Development

LENCAPAVIR

- Capsid inhibitor with slow release injection potential.
- Capsid: cone shaped structural core of the HIV virion that protects HIV RNA and related enzymes, primarily composed of p24.
- The capsid initially breaks down within CD4 cells (releasing p24) and then re-combines when new particles are formed.
- L can block <u>both</u> disassembly and assembly (resistance).





LENCAPAVIR

- Currently formulated as a long-acting SQ injection (q12week dosing).
- Active against multiple resistant HIV variants.
- PO dosage form with less frequent dosing now under development.
- Resistant escape variants have decreased viral fitness.

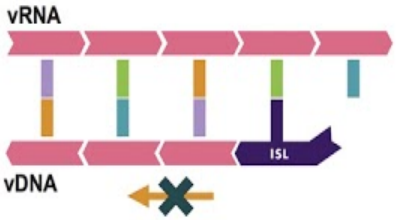
ISLATRAVIR

- Nucleoside reverse transcriptase translocation inhibitor.
- Multiple MOA that lend to increased potency.
- Prevents nucleotide binding AND translocation (NRTIs only prevent cause chain termination – translocation still possible).
- Long intracellular half-life with efficacy against most resistant strains (including NRTIs).
- Phase 2 trial in combination with Doravirine (potential 2 drug regimen).

What is Islatravir (ISL)?

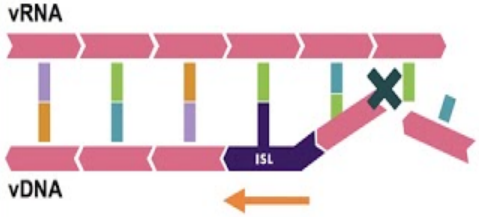
- NRTTI: nucleoside reverse transcriptase translocation inhibitor

Translocation Inhibition



- Translocation inhibition prevents opening of the RT nucleotide binding site
- Nucleotides cannot be incorporated into vDNA
- **Viral replication is inhibited**

Delayed Chain Termination



- ISL changes vDNA structure such that nucleotide incorporation is prevented
- As ISL is not in the RT active site, it is not susceptible to resistance-conferring mutations
- **Viral replication is inhibited**

Source: McComsey G, et al. CROI 2020. Abstract 686.

Novel Integrase Inhibition

- Targeting new binding sites on the integrase enzyme.
- Potential to circumvent RAL resistant variants.
- Likely long acting oral or IM agents.

VPU Inhibitors

- VPU = Viral Protein U
- Role in release of infectious particles from cells.
- Found in cell membranes of infected cells.
- Viroproin protein that can permeabilize membranes.

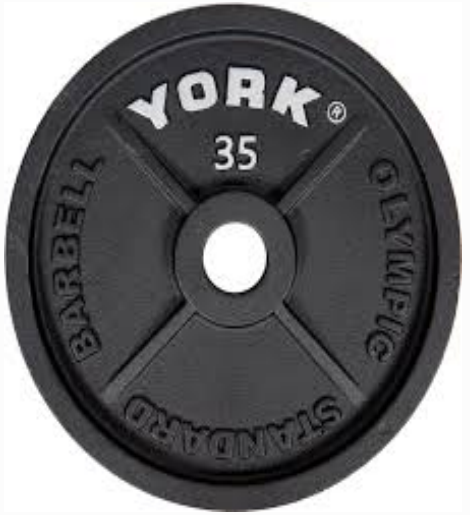
- BIT225 (immune modulating effects = conversion to a non-progressor?)
- Add-on to ART?

Broadly Neutralizing Antibodies

- Naturally occurring bNAbs can lower VL by 1.5 $\log_{10}$ (half-life 2-3 weeks)
- Combination of multi-faceted bNAbs as a new therapeutic approach
- Plagued with issues related to immune responses and resistance
- Time and concentration dependent?

Long-Acting Agents

- Cabotegravir and Rilpivirine LA [oral to IM] (INSTI & NNRTI)
- Lipid nano-formulated Tenofovir DP
- VN-1500-LAI (NNRTI)



CURE

 # People Living with HIV in 2019
38 million

 # People newly HIV-infected in 2019
1.7 million

 # AIDS related deaths in 2019
690 K

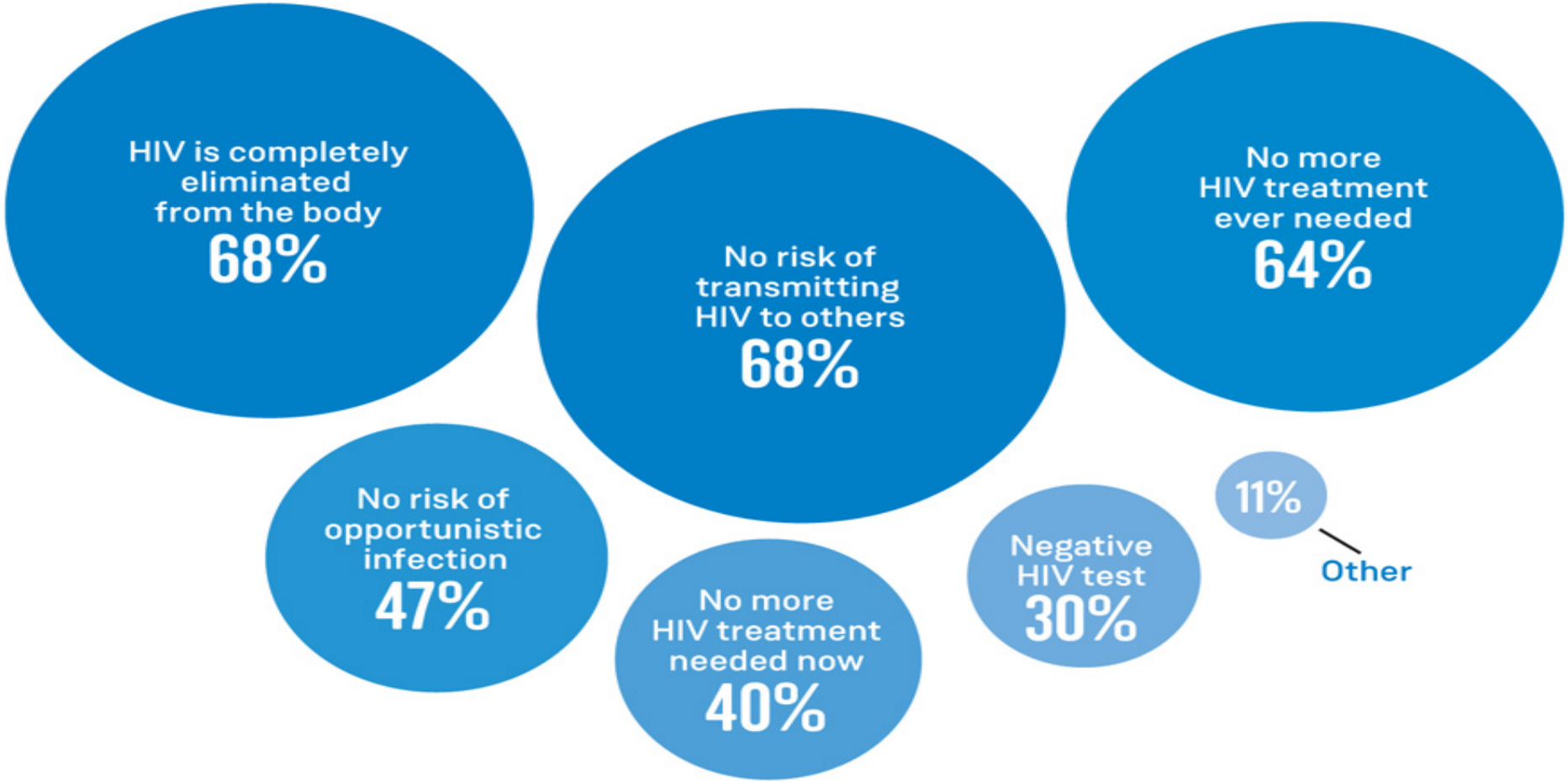
38,000,000 INFECTED

23,000,000 on cART

3 CURED (BMT)

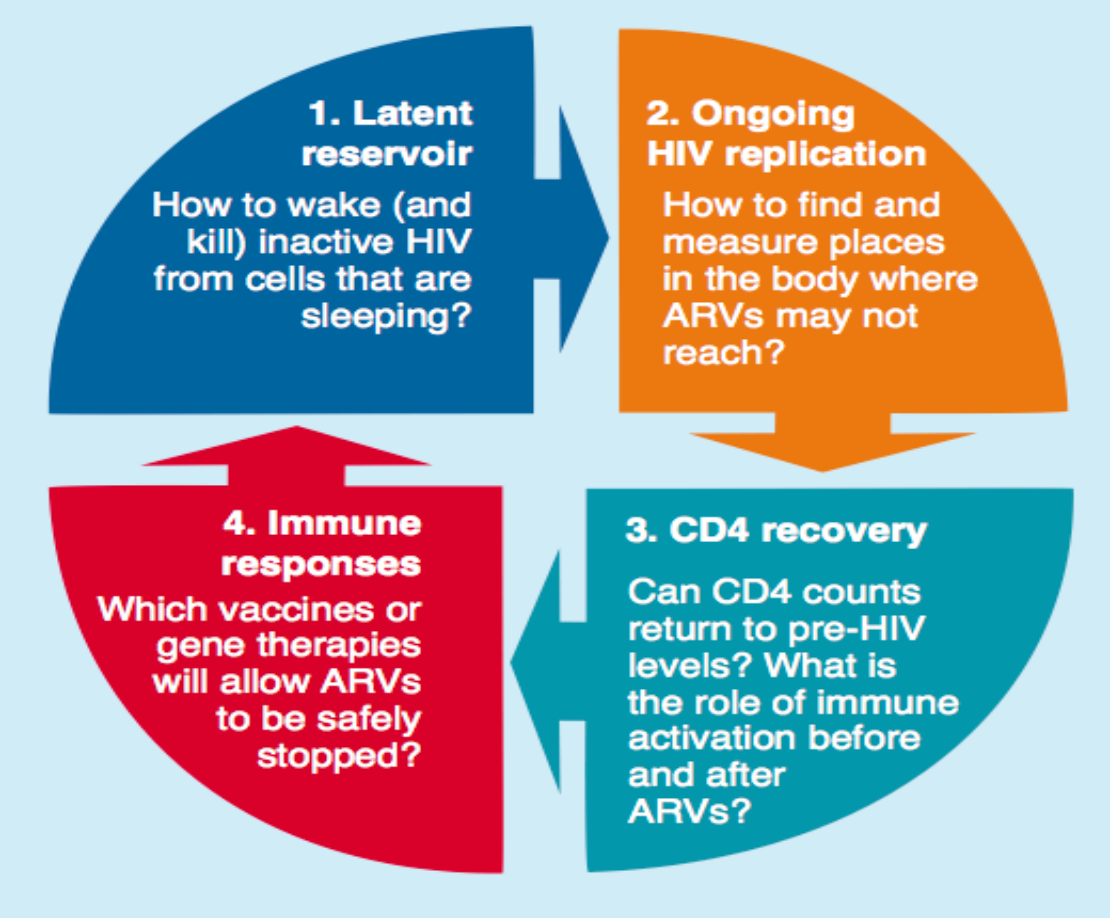
WHAT DOES A 'CURE FOR HIV' LOOK LIKE?

397 PEOPLE LIVING WITH HIV IN THE U.S. SURVEYED. (RESULTS EXCEED 100% BECAUSE RESPONDENTS WERE ALLOWED TO SELECT MORE THAN ONE ANSWER.)



https://www.positivelyaware.com/articles/what-does-hiv-cure-mean-you

The CURE Cycle



Latent Reservoir of Infected Cells = Pandora's Box

- Increasing efforts aimed at quantifying viremia within the latent reservoir
- Therapeutics will rely on accurate measurements

- Culture Based Viral Outgrowth Assay (underestimation)
- Total HIV DNA (overestimation)

- IPDA (**Intact** Proviral DNA Assay)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6447073/

CURE Strategies

Latent Reservoir of Infected Cells = Pandora's Box

- 'Shock and Kill'

  [histone deacetylase inhibitors to kill; a fourth or novel ARV to kill]

- bNAbs (prevent infection and/or target infected cells for killing)

Weight Gain

- Relatively new adverse effect associated with ARVs

Pregnancy

- Naturally occurring

Prevention

- Cabotegravir vs TDF/FTC

  CAB PO x 5 weeks then IM q 60 days

  TDF/FTC PO QD

  CAB non-inferior, superior

  DSMB halted trial