PENTA-ID INVESTIGATORS' MEETING 2017

New strategies, new drugs

Tim Niehues
HELIOS Klinikum Krefeld, Germany

April 28° 2017
San Servolo, Venice

Slights by

Christian Hoffmann, Hamburg

Pablo Rojo, Madrid

aidsinfo.nih.gov/understanding-hiv-aids/fact-sheets

www.iasusa.org/content/barriers-hiv-cure

(J. Siciliano, 15.4.2016)

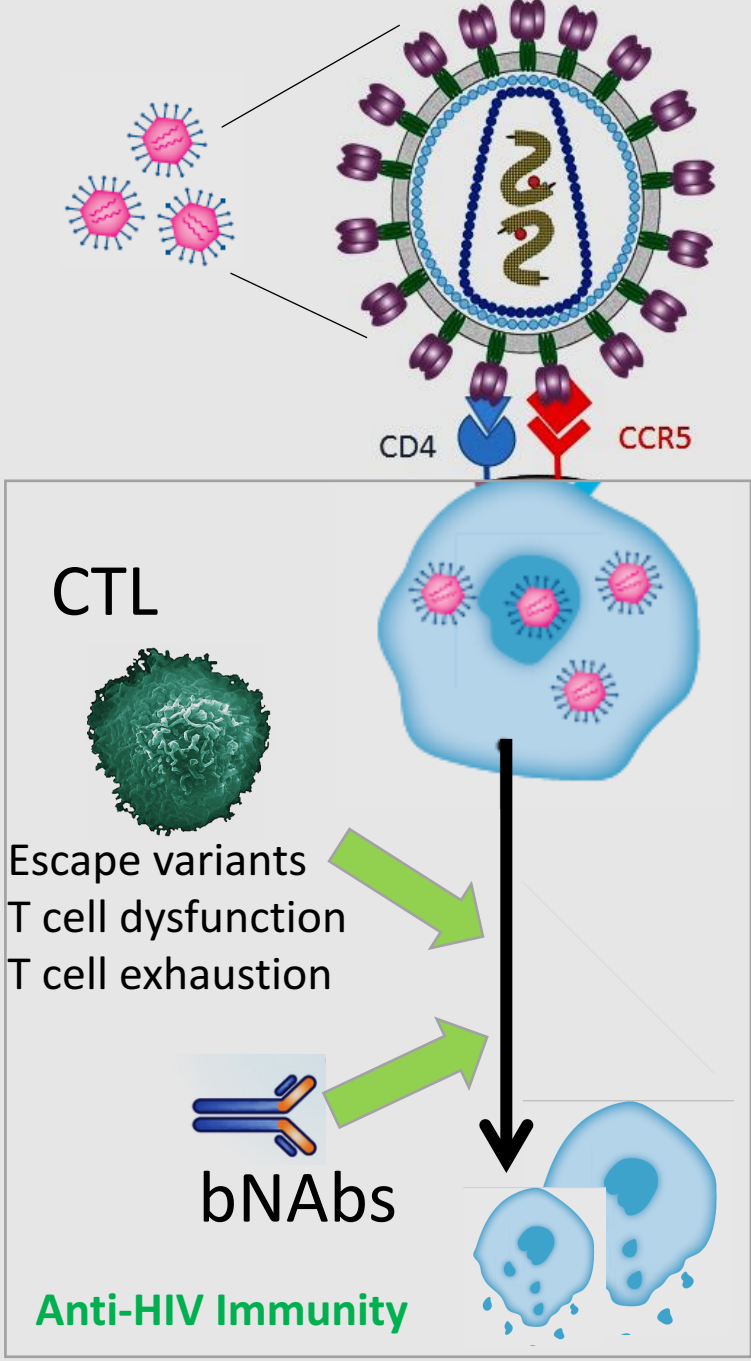
Questions adressed

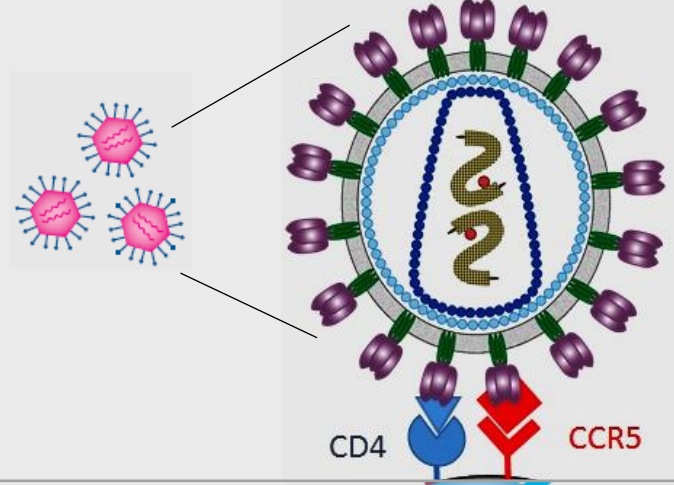
What are the current barriers to cure?

What are the current cure strategies in general?

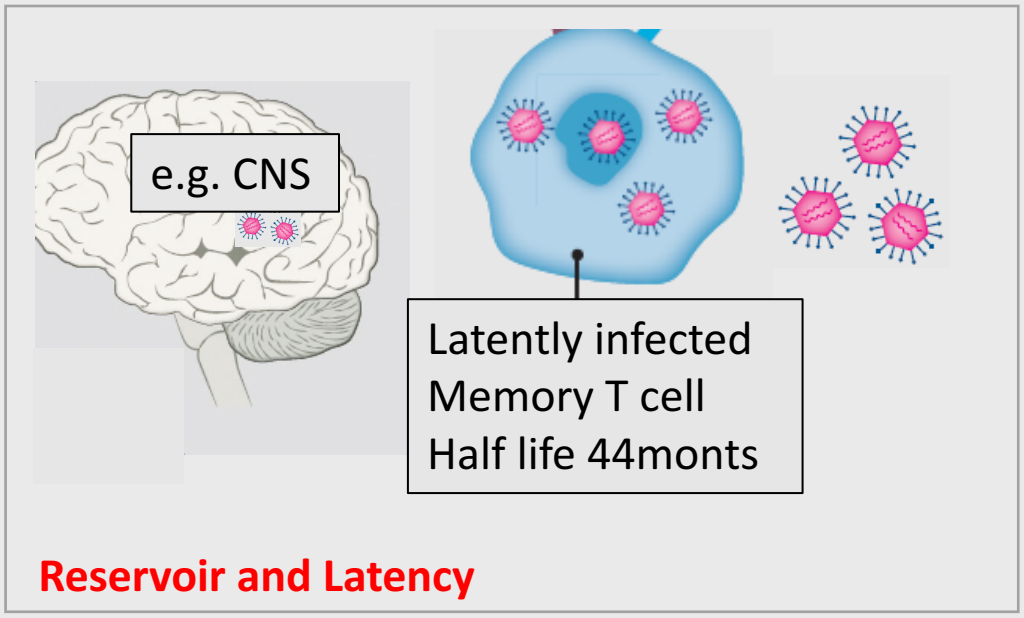
Which new drugs are available?

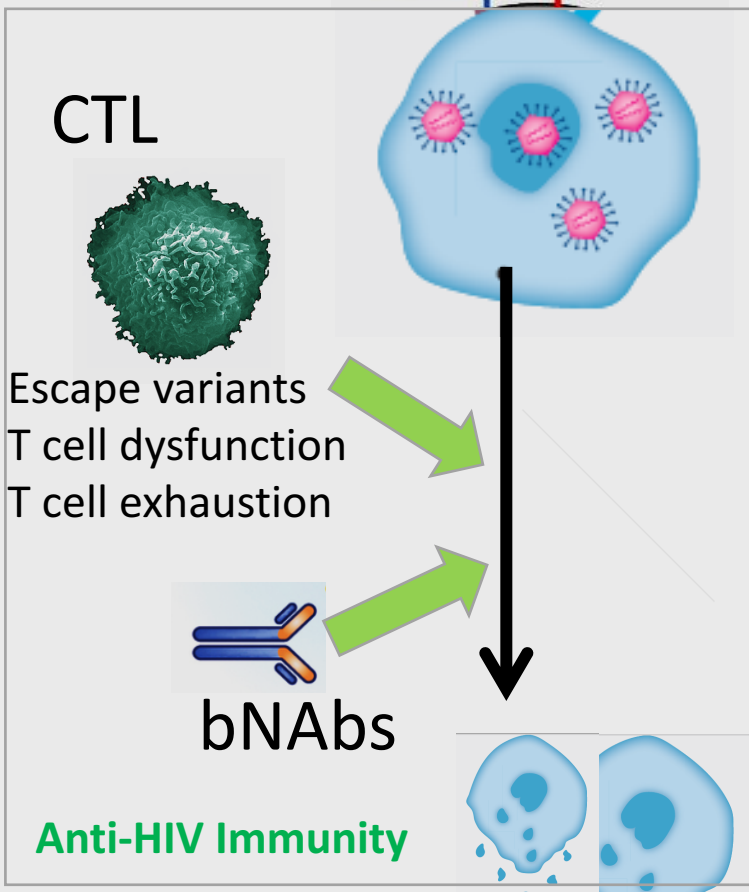
How does this apply to children?


CD4
CCR5
CTL
Escape variants
T cell dysfunction
T cell exhaustion
bNAbs
Anti-HIV Immunity



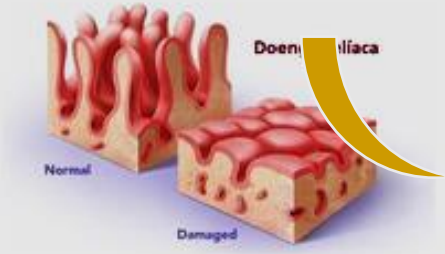
ANATOMICAL BARRIER



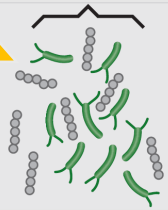


Immune deficiency

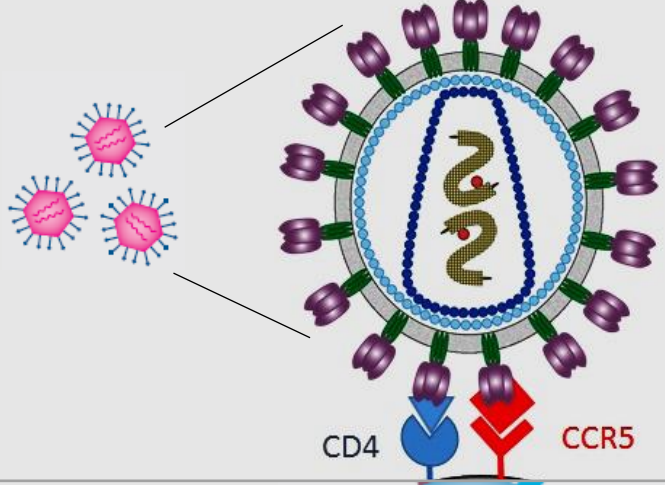
Mucosal damage and translocatin of bacteria



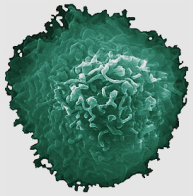
Activation of infected cells



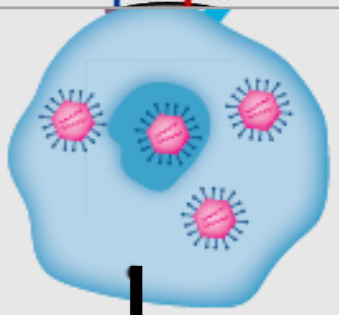
Immune activation



CTL

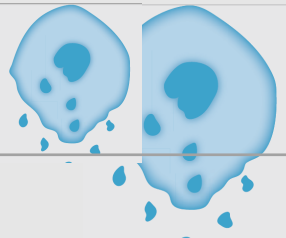


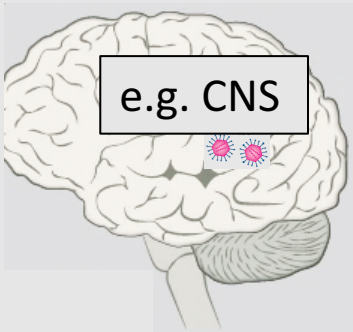
Escape variants
T cell dysfunction
T cell exhaustion

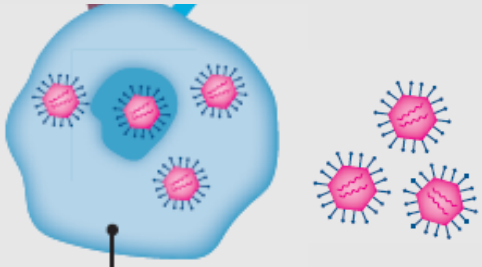


bNAbs

Anti-HIV Immunity







Latently infected
Memory T cell
Half life 44monts

Reservoir and Latency

Questions adressed

What are the current barriers to cure?

What are the current cure strategies in general?

Which new drugs are available?

How does this apply to children?

Cure

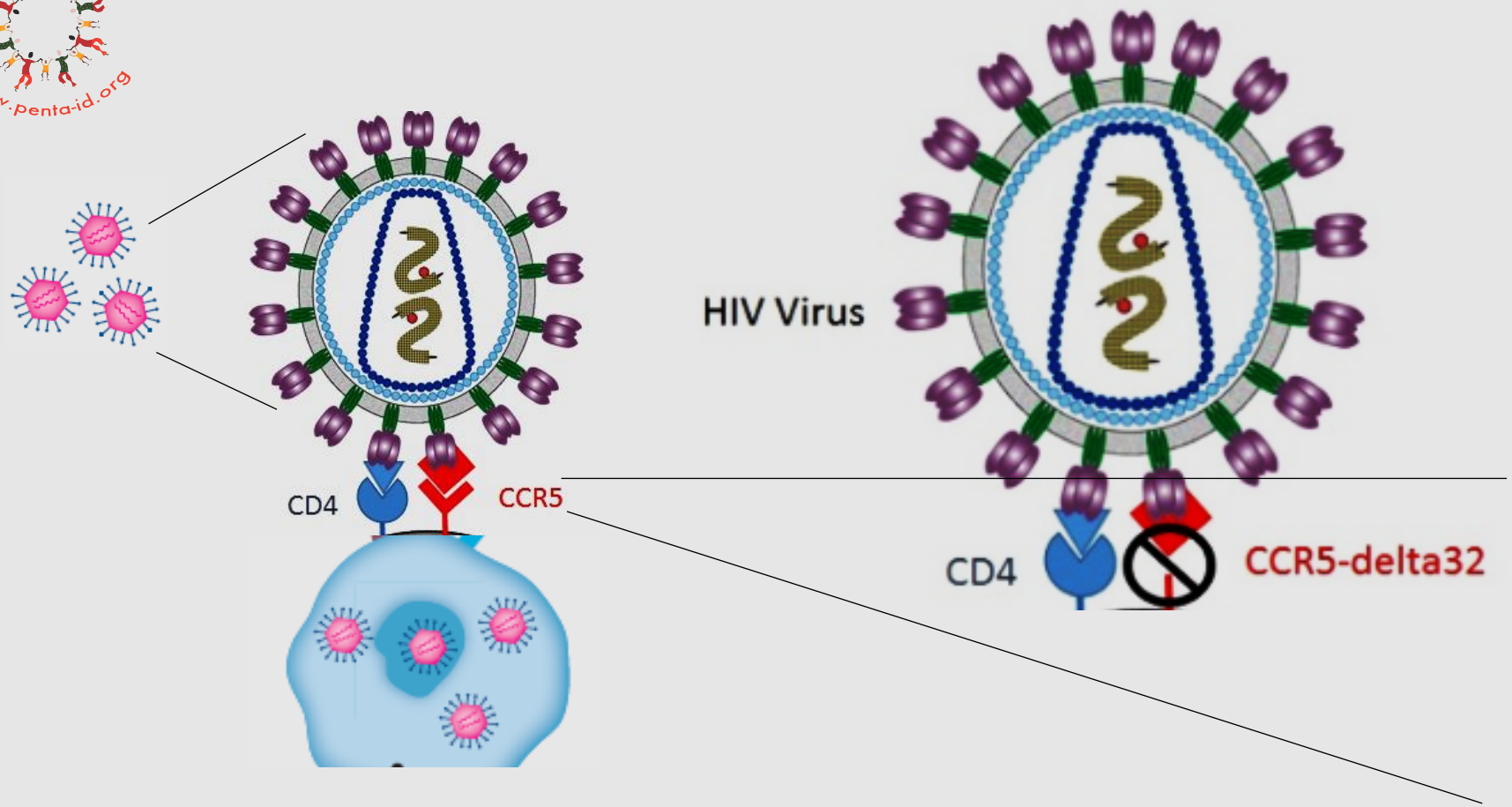
= control of viral replication in absence of ART

Eradication Cure = elimination of all reservoirs

Functional Cure = control of viral replication without reservoir eradication

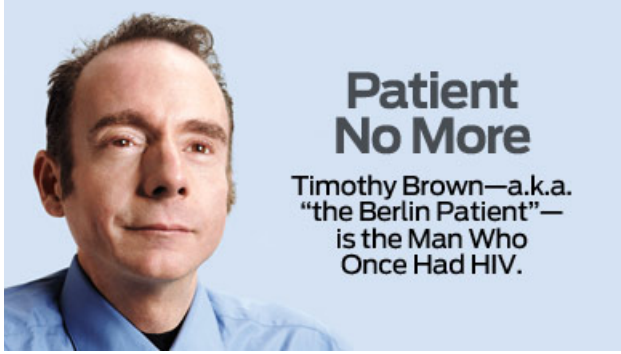
Hybrid Cure = reduction of the reservoir + boosting immune responses

NO Infection



Eradication Cure Berlin Patient

Hütter, N Engl J Med 2009, 360:692-698.



1995 Diagnosis HIV in 1995; ART

2007-2008 Two times conditioning for stem cell transplants for Acute myeloid leukemia AML, (destroys reservoir)

Donor with "delta 32" CCR5 receptor homozygous mutation (prevents reinfection)

Stopped taking ART day +1 of first transplant

Cure

= control of viral replication in absence of ART

Eradication Cure = elimination of all reservoirs

Functional Cure = control of viral replication without reservoir eradication

Hybrid Cure = reduction of the reservoir + boosting immune responses

Functional Cure
Host cell modification

Tebas. N Engl J Med 2014, 370:901-910;

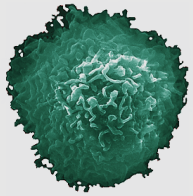
Conditioning and engraftment of single dose 10 billion zinc-finger modified CCR5 deficient autologous CD4+ T cells (n=12 open-label, nonrandomized, uncontrolled study in aviremic HIV infection) while on ART

ART interruption (n=6): decline in circulating

CCR5-modified cells (−1.81 cells per day) was significantly less than the decline in unmodified cells (−7.25 cells per day) (P = 0.02).

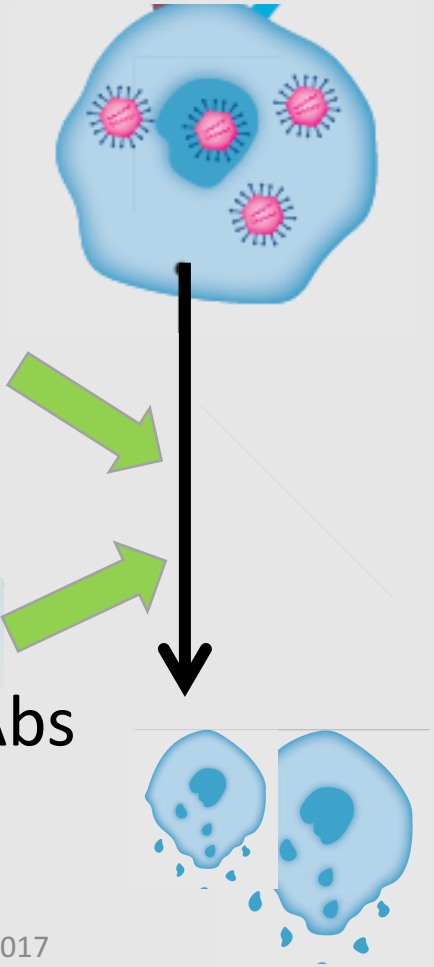
Functional Cure
Designer immune responses

Engineered
T cells with
Chimeric
Antigen
Receptors
(CAR T Cells)



Heterologous
Neutralizing
Antibodies

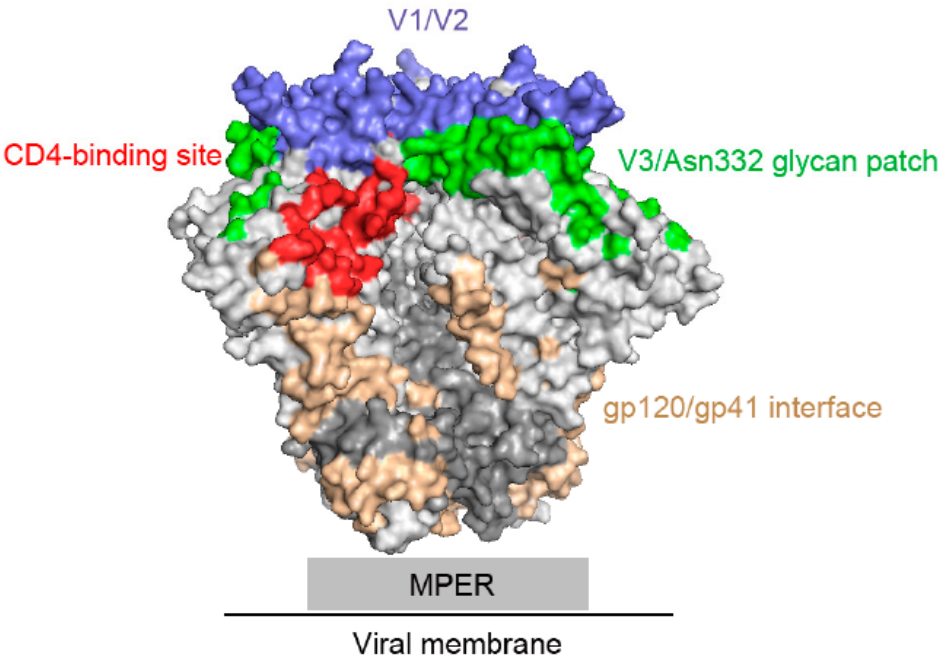
bNAbs



Functional Cure
Designer immune responses

Heterologous Broadly neutralizing antibodies bNAbs

Int. J. Mol. Sci. **2016**, 17, 1901;



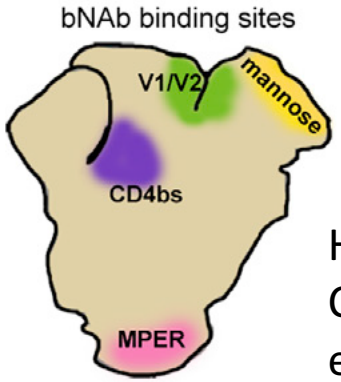
Target Sites (See Figure 1)	bNAb	Research & Development Stage
CD4-binding site	VRC01	Phase I
	3BNC117	Phase II
V1/V2	PGDM1400	Preclinical
V3/Asn332 glycan patch	PGT121	Preclinical
	10-1074	Phase I
gp120/ gp41-interface	PGT151	Preclinical
	35O22	Preclinical
	8ANC195	Preclinical
MPER	10E8	Preclinical

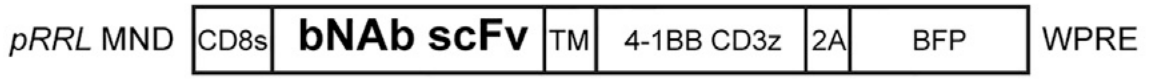
Functional Cure
Designer immune responses

Chimeric antigen receptor (CAR) expressing effector cytotoxic T lymphocytes targeting HIV-1

Hale et al. Molecular Therapy Vol. 25 No 3 March 2017

bNAb-based single-chain variable fragments fused to second-generation CAR signaling domains, delivered directly into the CCR5 locus of T cells by gene editing (prevents infection of effectors)

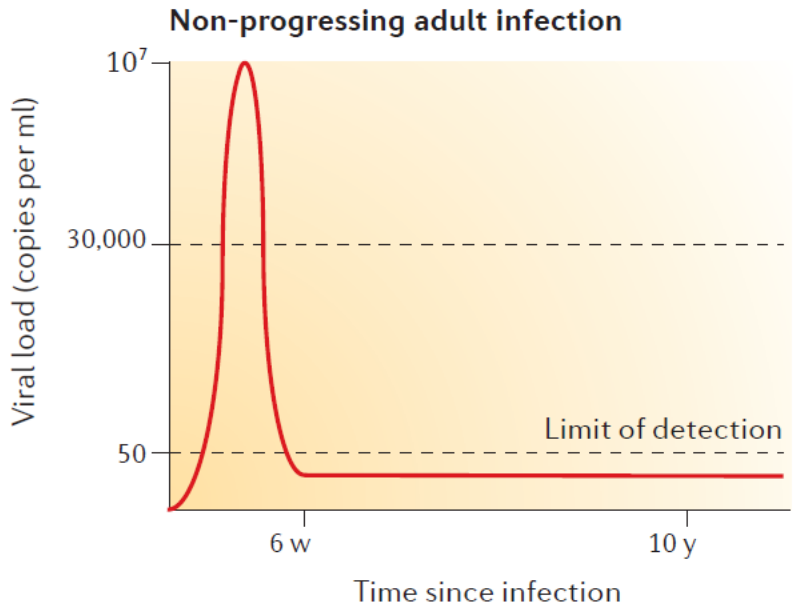


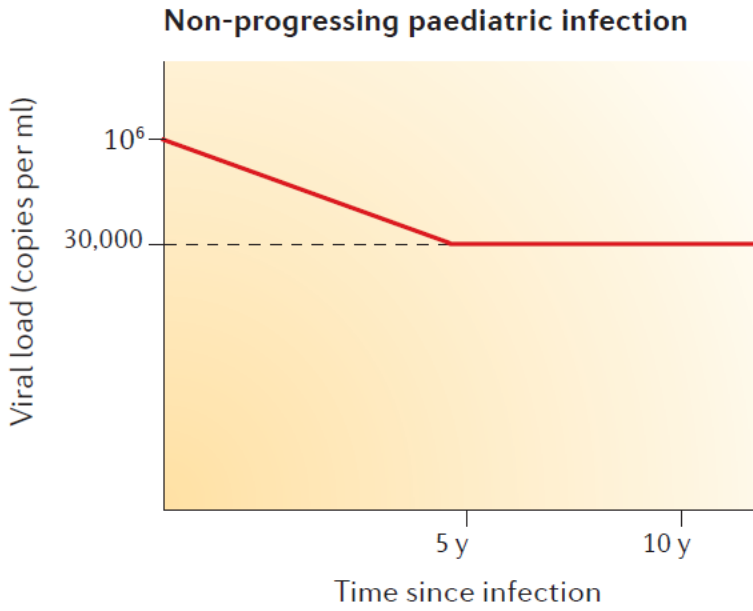


HIV envelope. V1/V2, variable loops 1 and 2; mannose, CD4bs, CD4 binding site; MPER, membrane proximal external region.

Functional Cure

Boost own host immune responses
"Salutogenesis" (as opposed to pathogenesis)





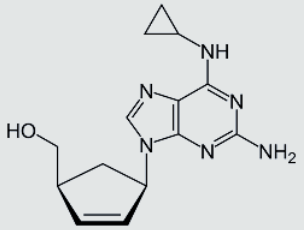
CMV-vectored HIV vaccine could control viremia following challenge and eliminate virally-infected cells

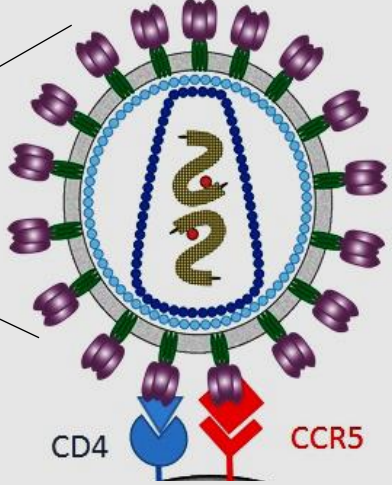
(SIV animal model; Hansen Nature 2011, 473:527)

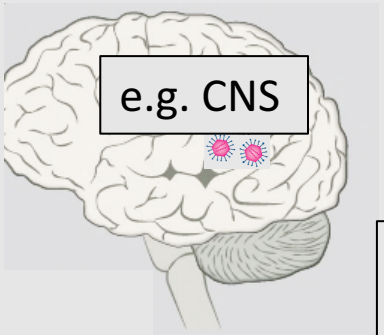
Conclusions I

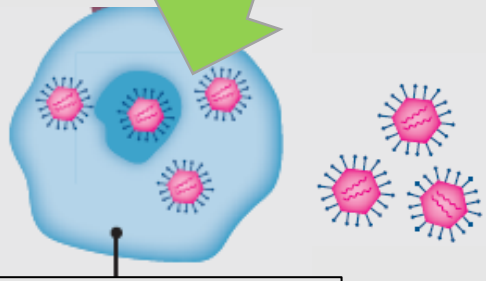
- Eradication is the exception
- Host cell editing advanced to clinical stage
- bNAbs moving at clinical stage
- Designer Immunology plus understanding own immunity better might supplement current approaches

HAART+









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Questions adressed

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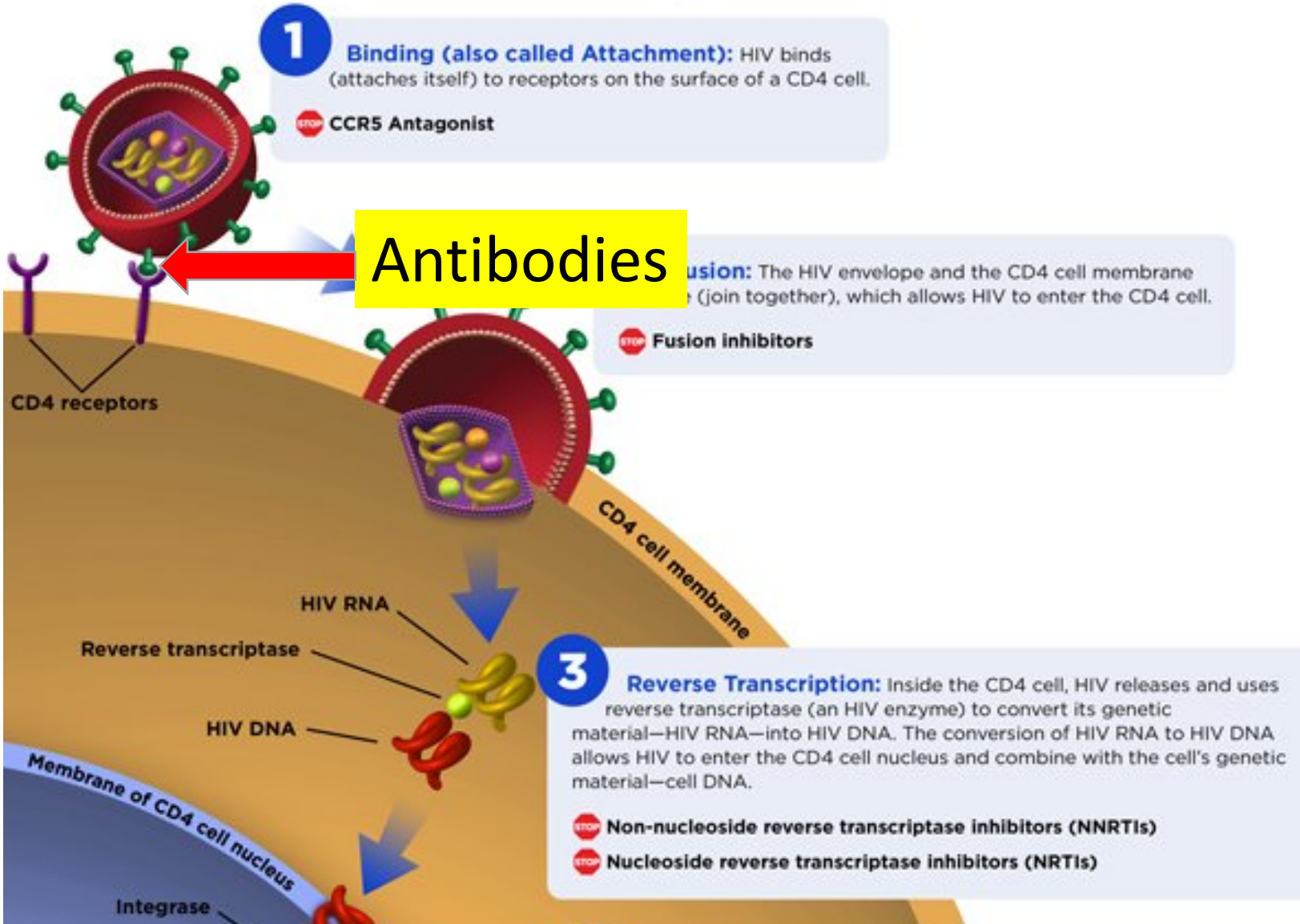
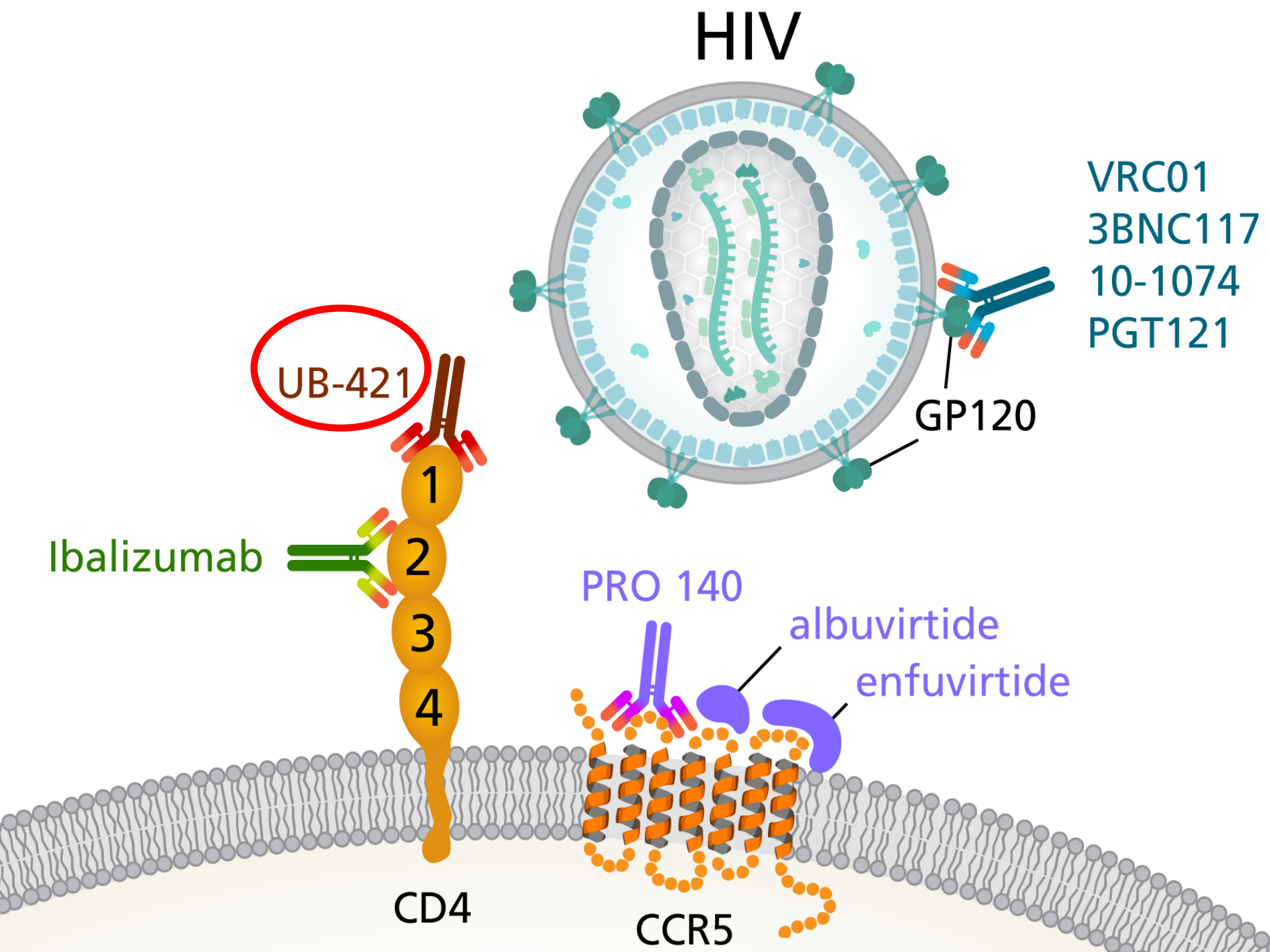
Functional cure: New Drugs CROI 2017




HIV
VRC01
3BNC117
10-1074
PGT121
GP120
UB-421
1
2
3
4
Ibalizumab
PRO 140
albuvirtide
enfuvirtide
CD4
CCR5

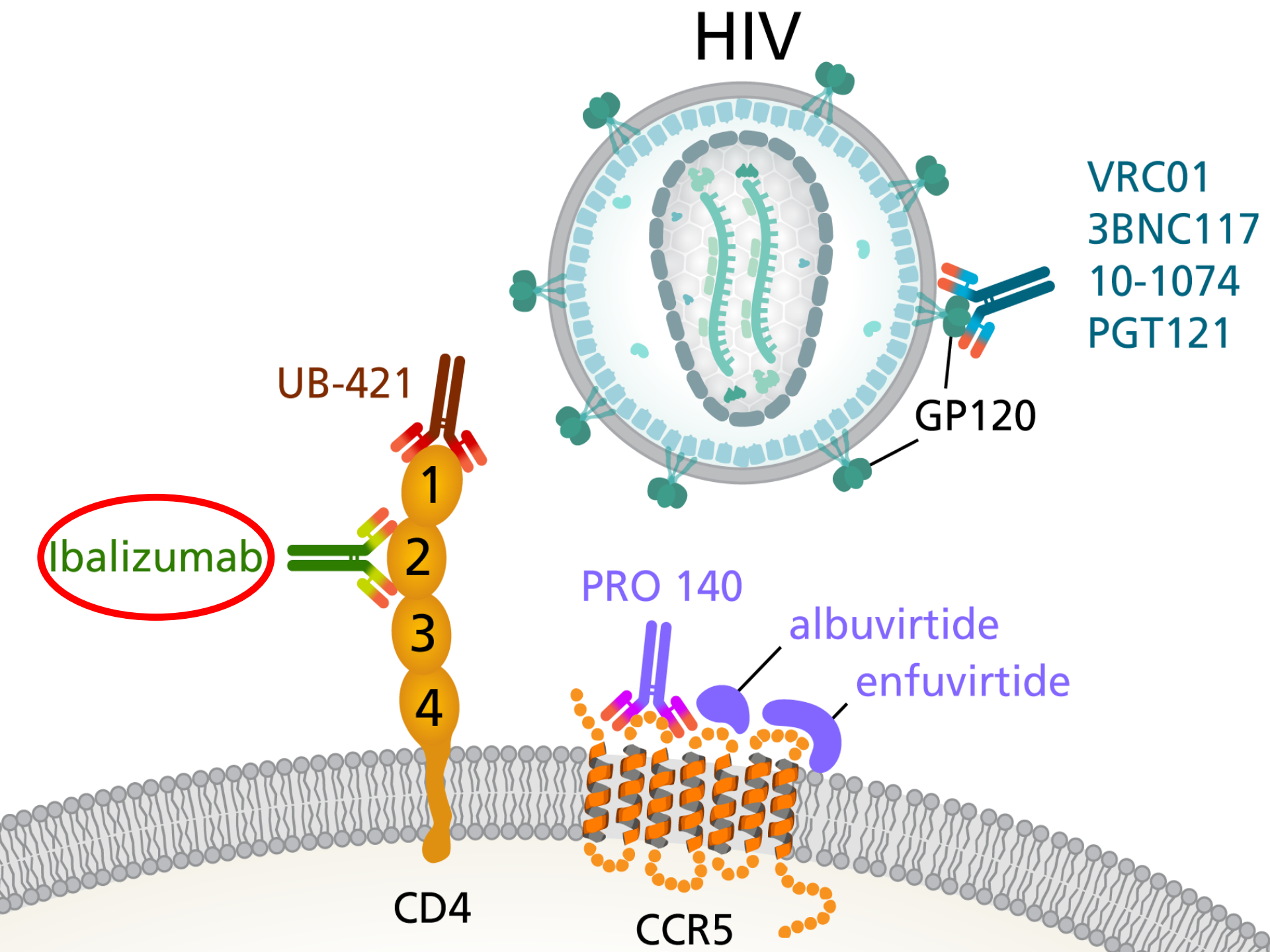
UB-421

binds CD4 receptor, blocks HIV-1entry

Phase 2a; n=29 antiretroviral-naïve adults (Taiwan; 8-week monotherapy; 10 or 25mg/Kg/weekly or biweekly)
VL reduction: 2.27 (0.6) / 2.45 (0.46) log10 copies/mL
Adverse event: mild/moderate rash (48.3% of 29 subjects)

Monotherapy in virally suppressed HIV-1 adults?

Wang CY et al # 450 LB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albuvirtide
enfuvirtide
CD4
CCR5

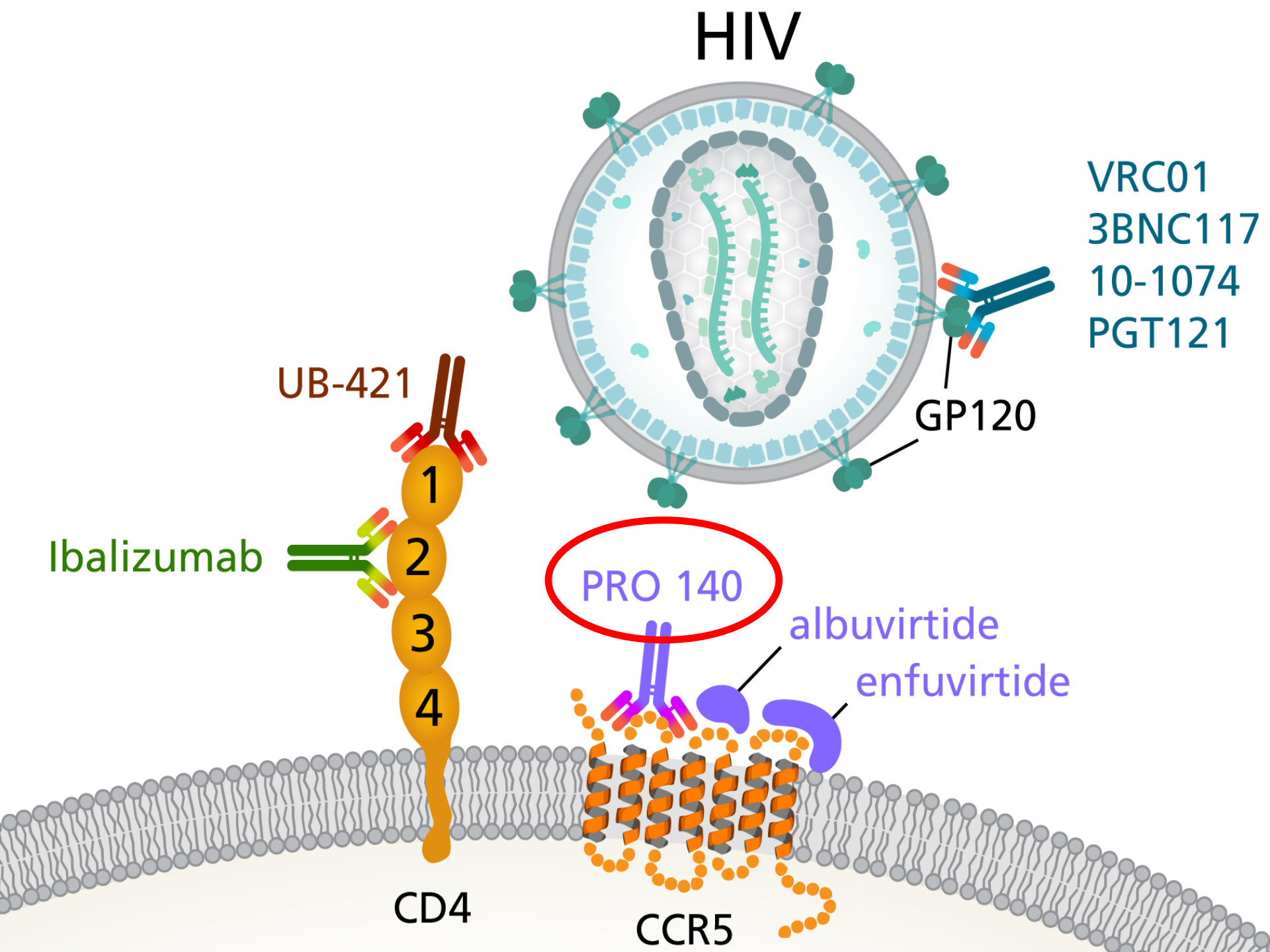
Ibalizumab (IBA)

humanized monoclonal antibody binds CD4, blocks viral entry

antiviral activity and safety of IBA plus an optimized background regimen (OBR) in treatment-experienced patients with MDR HIV-1 (n=40)

Bi-weekly IBA plus OBR maintained virologic efficacy and well tolerated through Wk 24 in multidrug resistant cases

Lewis S et al # 449LB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enfuvirtide
CD4
CCR5

PRO140

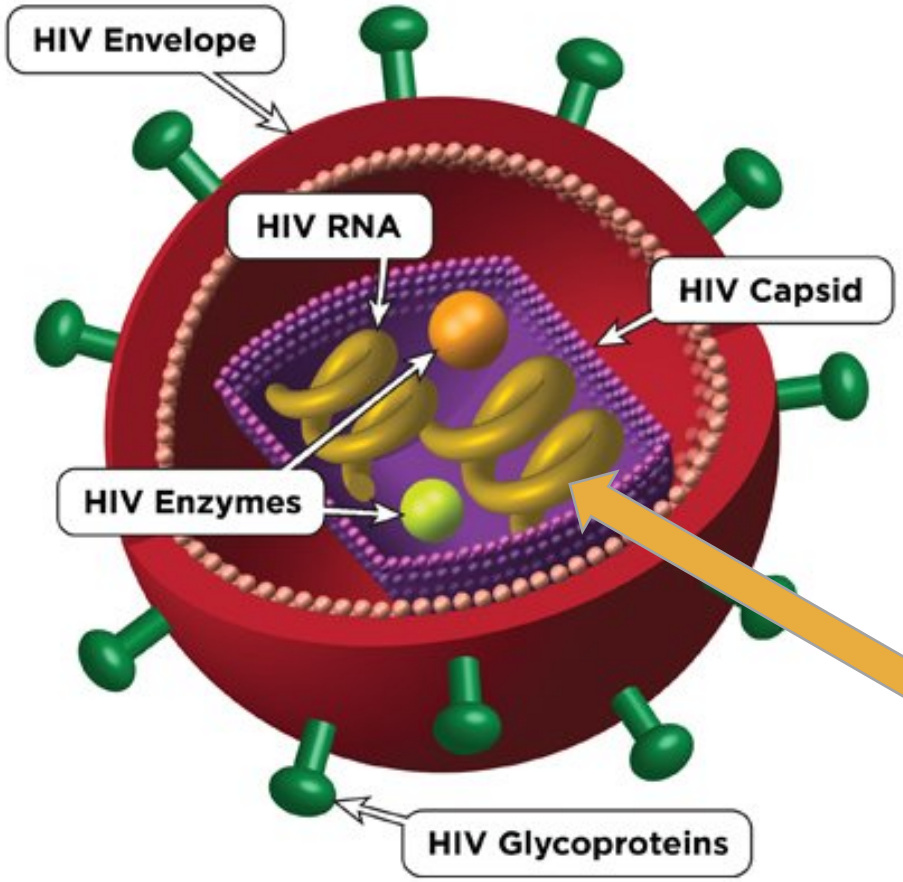
humanized CCR5 mAb

N=16; open-label, single-arm phase 2b extension study as monotherapy following initial ART by weekly self-administered PRO140 350 mg SC.

simple, long-acting, single-agent for maintenance therapy

Lalezari et al #473

New Drugs CROI 2017



Key to Terms

HIV capsid: HIV's bullet-shaped core that contains HIV RNA

HIV envelope: Outer surface of HIV

HIV enzymes: Proteins that carry out steps in the HIV life cycle

HIV glycoproteins: Protein "spikes" embedded in the HIV envelope

HIV RNA: HIV's genetic material

NEW SUBSTANCE
CLASS: Capsid Inhibitors
GS-CA-1

GS-CA-1

novel class HIV capsid inhibitors (CAIs)

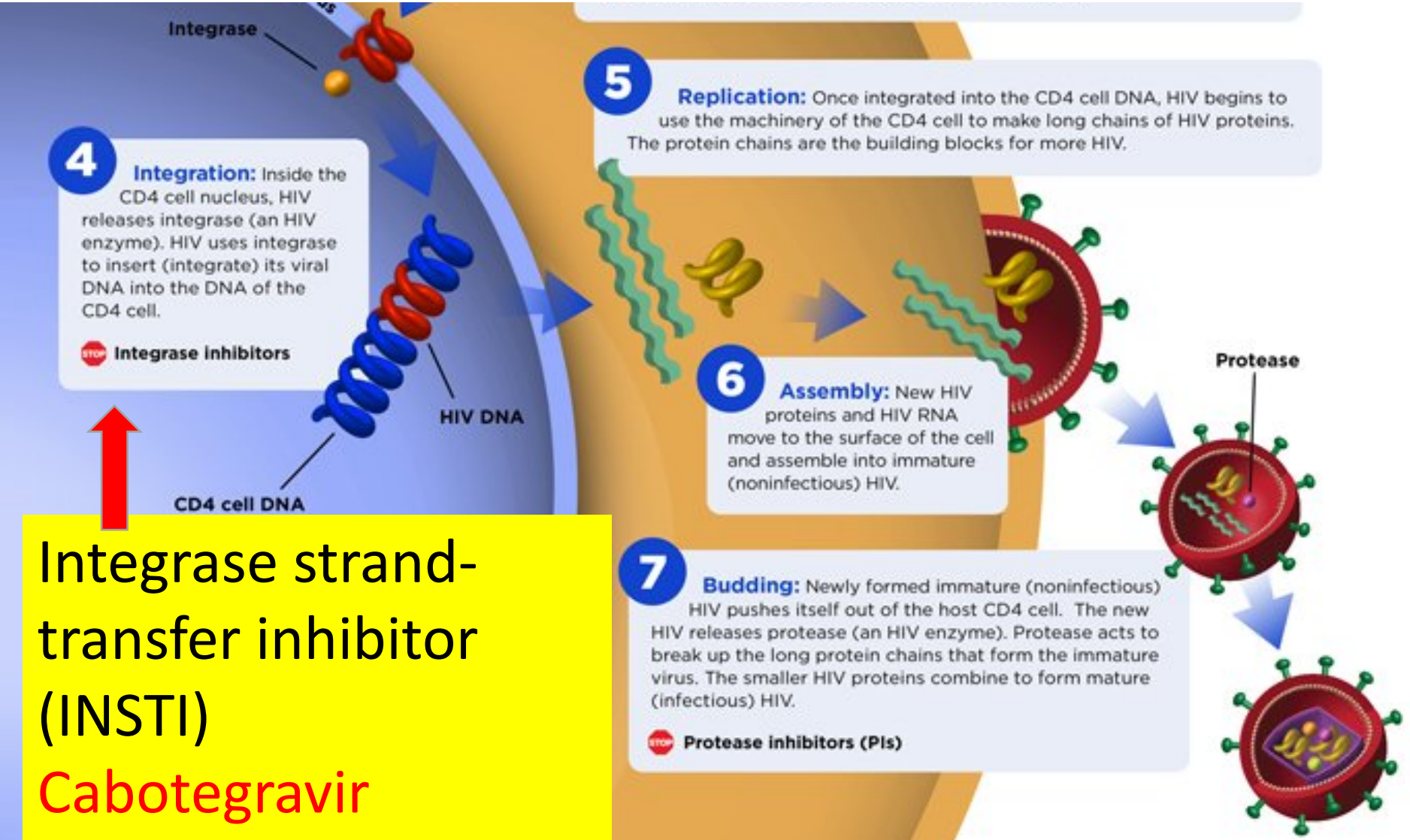
binds to a broadly conserved site at the interface of two adjacent monomers within a CA hexamer, interacts @ multiple sites with replication cycle

uniquely potent antiviral activity; potential as novel long-acting antiretroviral treatment

Tse WC et al # 38

Injectable long acting Drugs

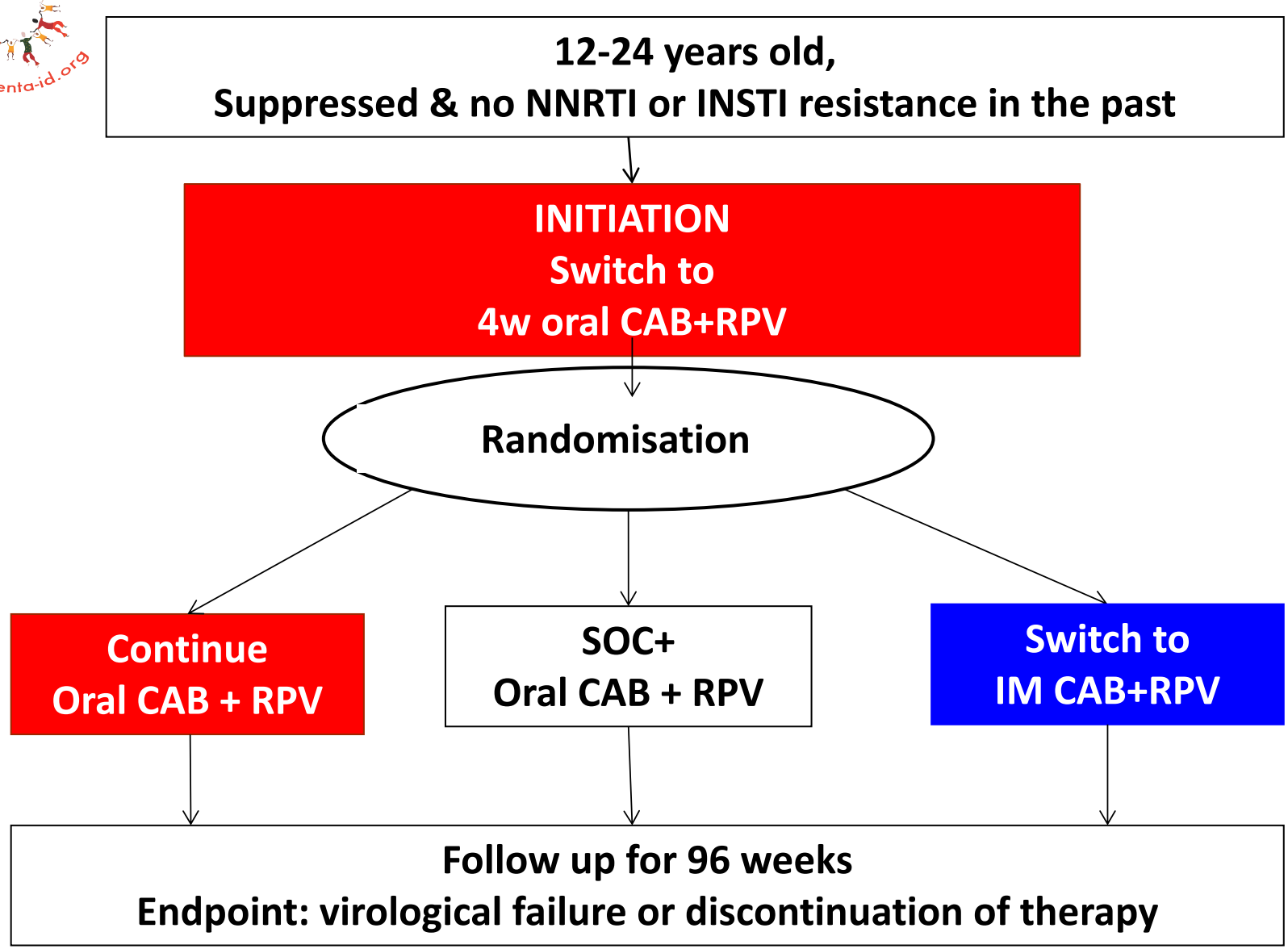
CROI 2016



Integrase strand-transfer inhibitor (INSTI)

Cabotegravir

Catching name



CAPIVARA

CAbotegravir
RiPIlVirine
Alternative Regimen for
Adolescents

Largest rodent in the world

Great swimmer, remains **completely submerged for up to five minutes**

Sleeps a lot in water, keeping only their noses out of the water.

Cure

= control of viral replication in absence of ART

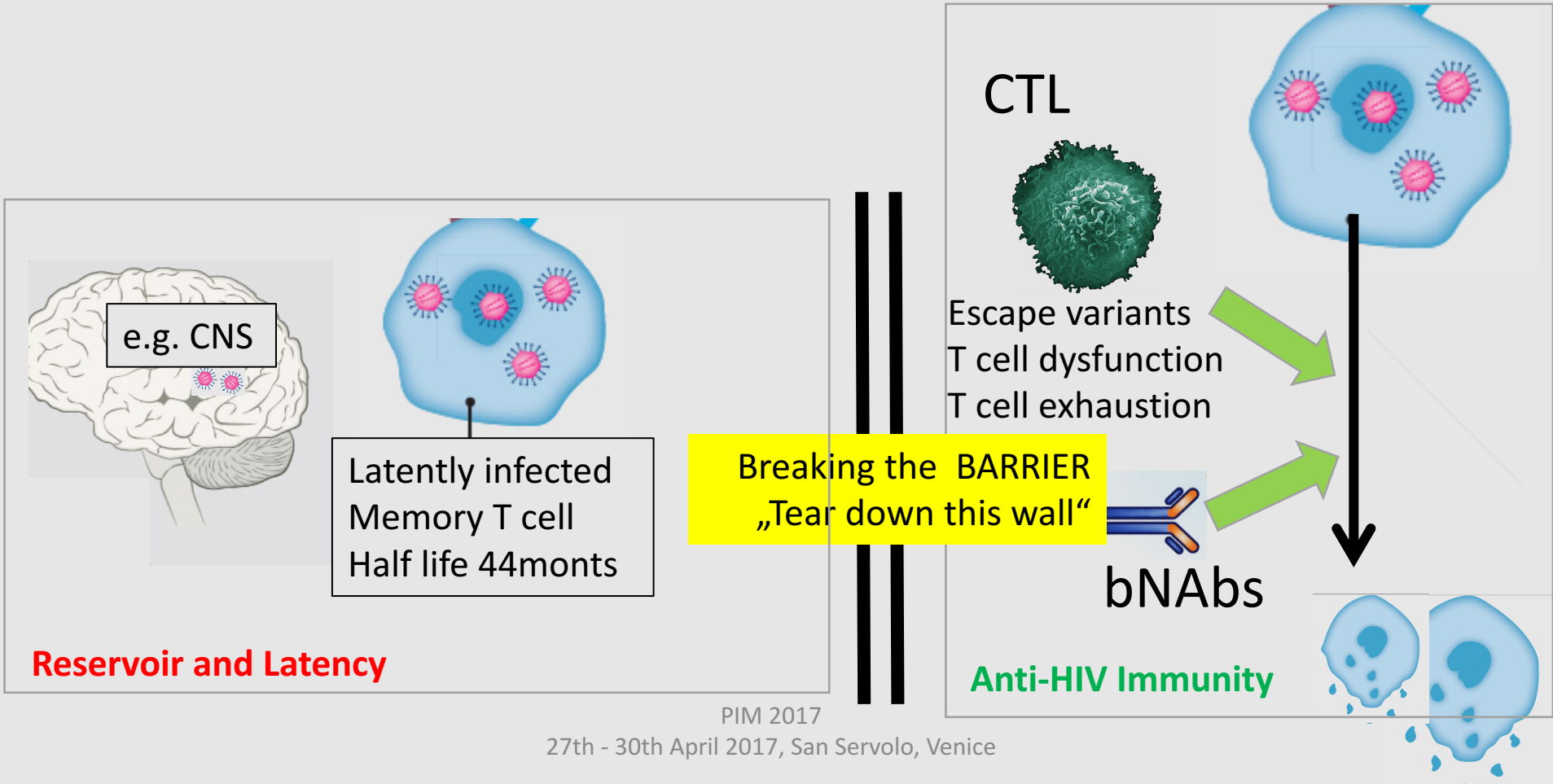
Eradication Cure = elimination of all reservoirs

Functional Cure = control of viral replication without reservoir eradication

Hybrid Cure = reduction of the reservoir + boosting immune responses

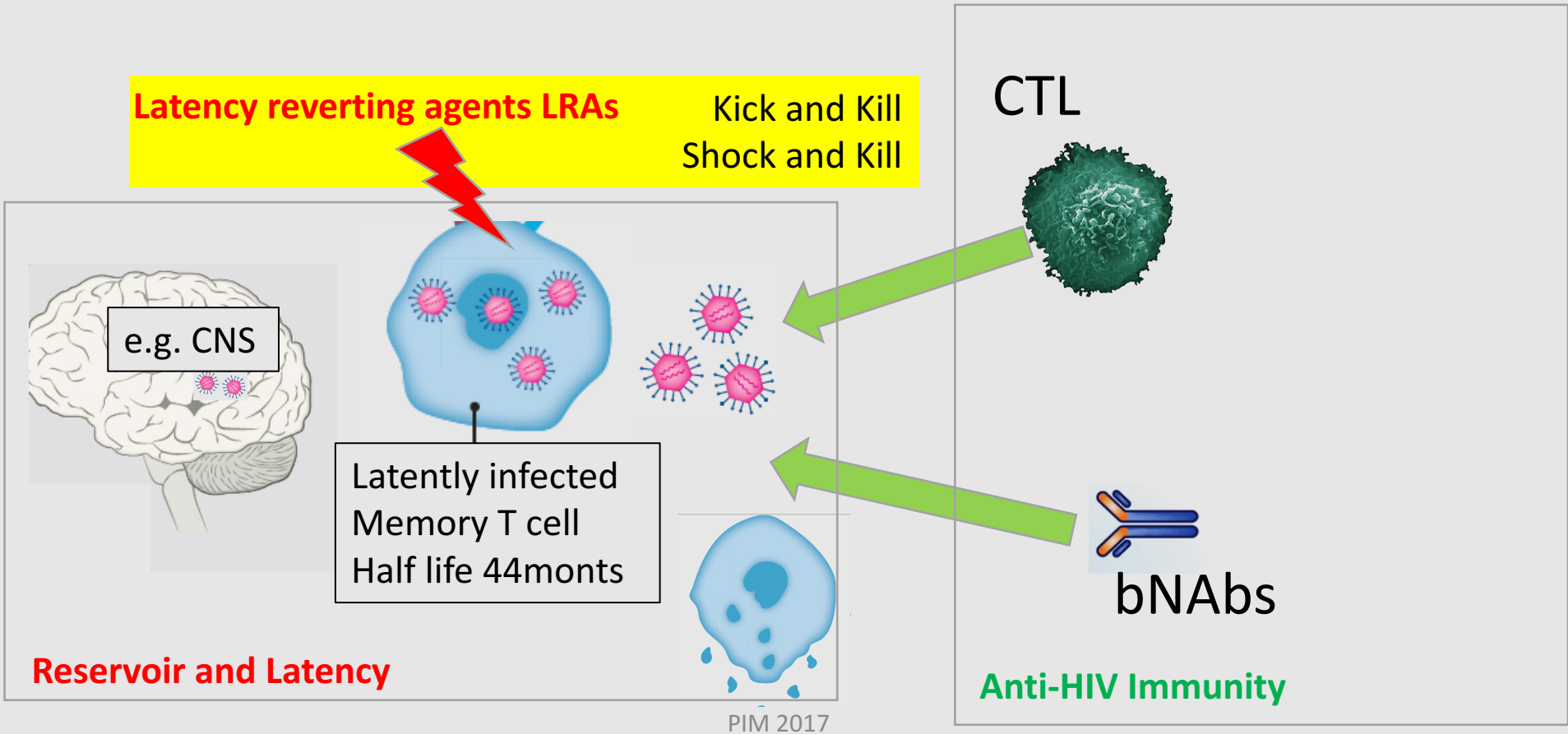
Hybrid Cure

reduction of the reservoir + boosting immune responses



Hybrid Cure

reduction of the reservoir + boosting immune responses



Hybrid Cure

reduction of the reservoir + boosting immune responses

Numerous LRAs identified in studies with transformed cell lines and primary T cell model systems

However, few work *ex vivo* with patient cells

Slight transient increases in plasma HIV RNA after LRA treatment (romidepsin, panobinostat, TLR7 agonist)

In clinical trials, no reduction in reservoir demonstrated yet

Conclusions II

- New drug class (CAI) may facilitate to hit even harder
- Long acting: multiple opportunities
- Hybrid cure by latency reversal (LRAs) not at clinical stage

Questions adressed

What are the current barriers to cure?

What are the current cure strategies in general?

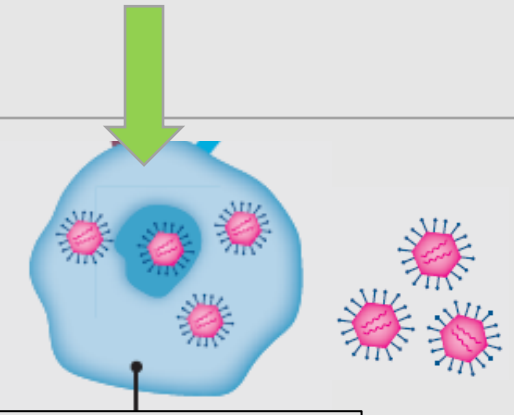
Which new drugs are available?

How does this apply to children?

Pediatric specific points vs. Adults Virology/Reservoir

HIV easy to identify early within hours after birth → HAART+

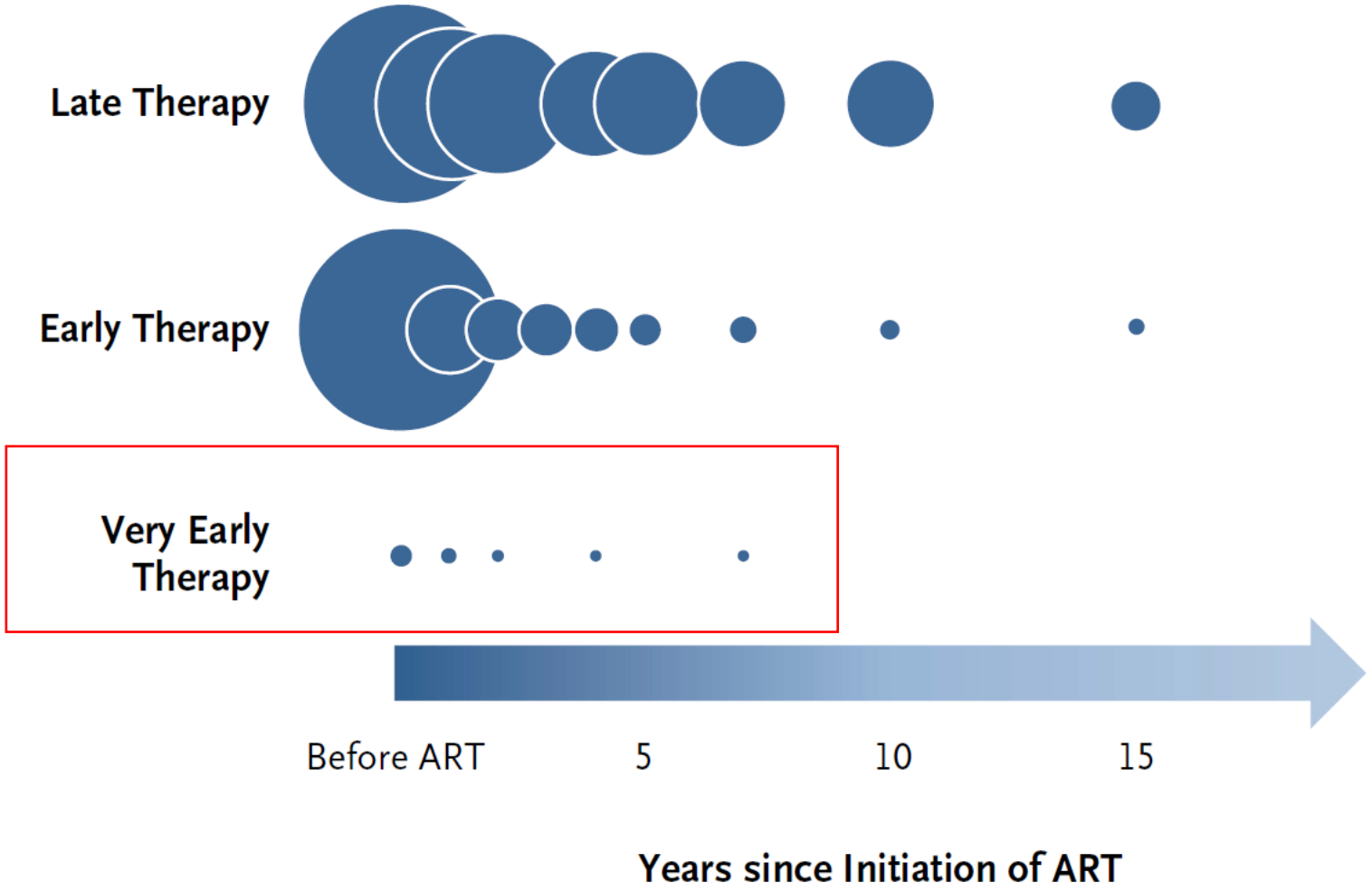
Seeding of viral reservoir (within 3 days of infection), might be prevented in children not in adults (earlier treatment possible)



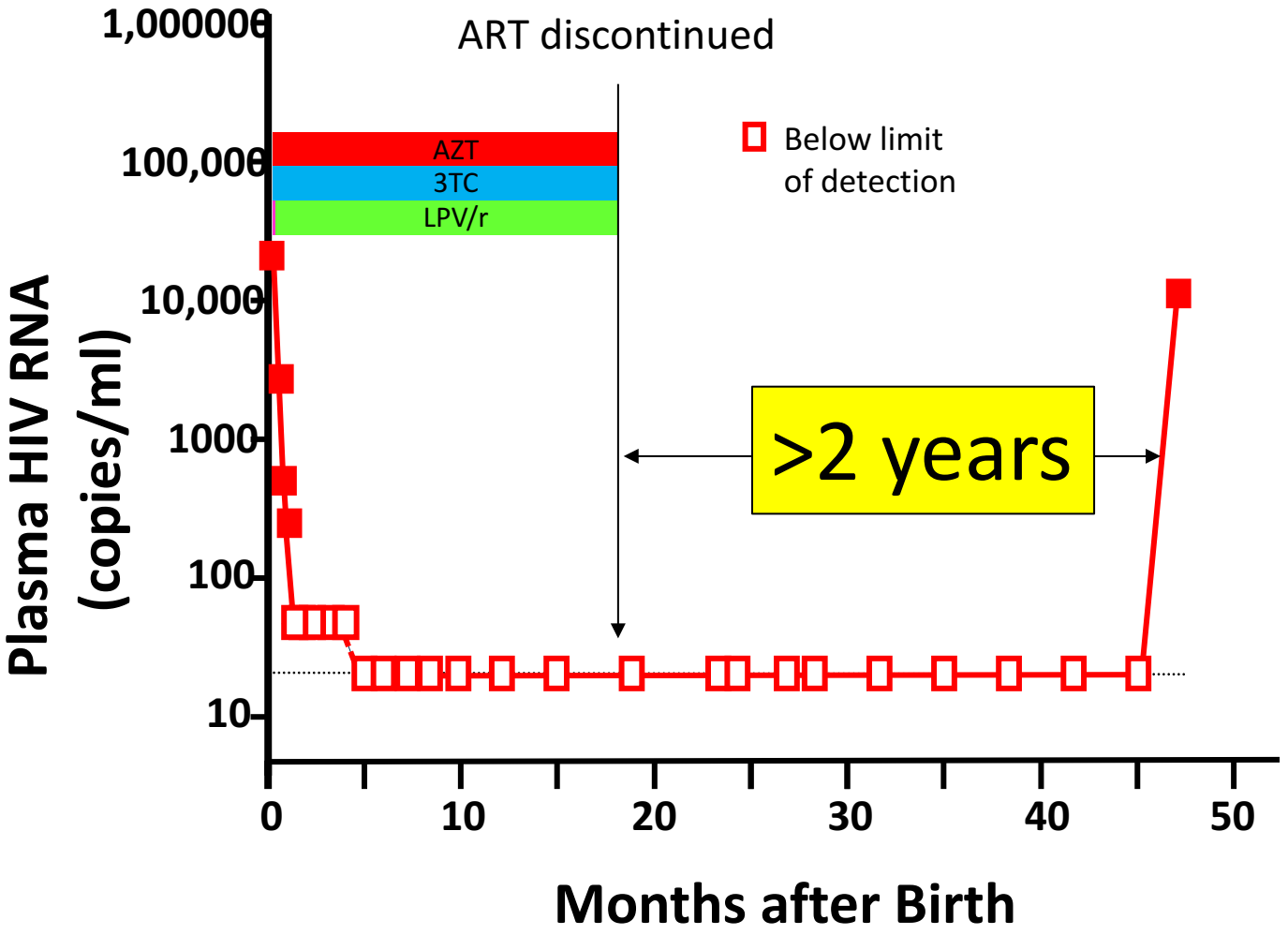
Reservoir and Latency

Size of total viral reservoir in relation to treatment start

Luzuriaga N Engl J Med 2016;374:761-70



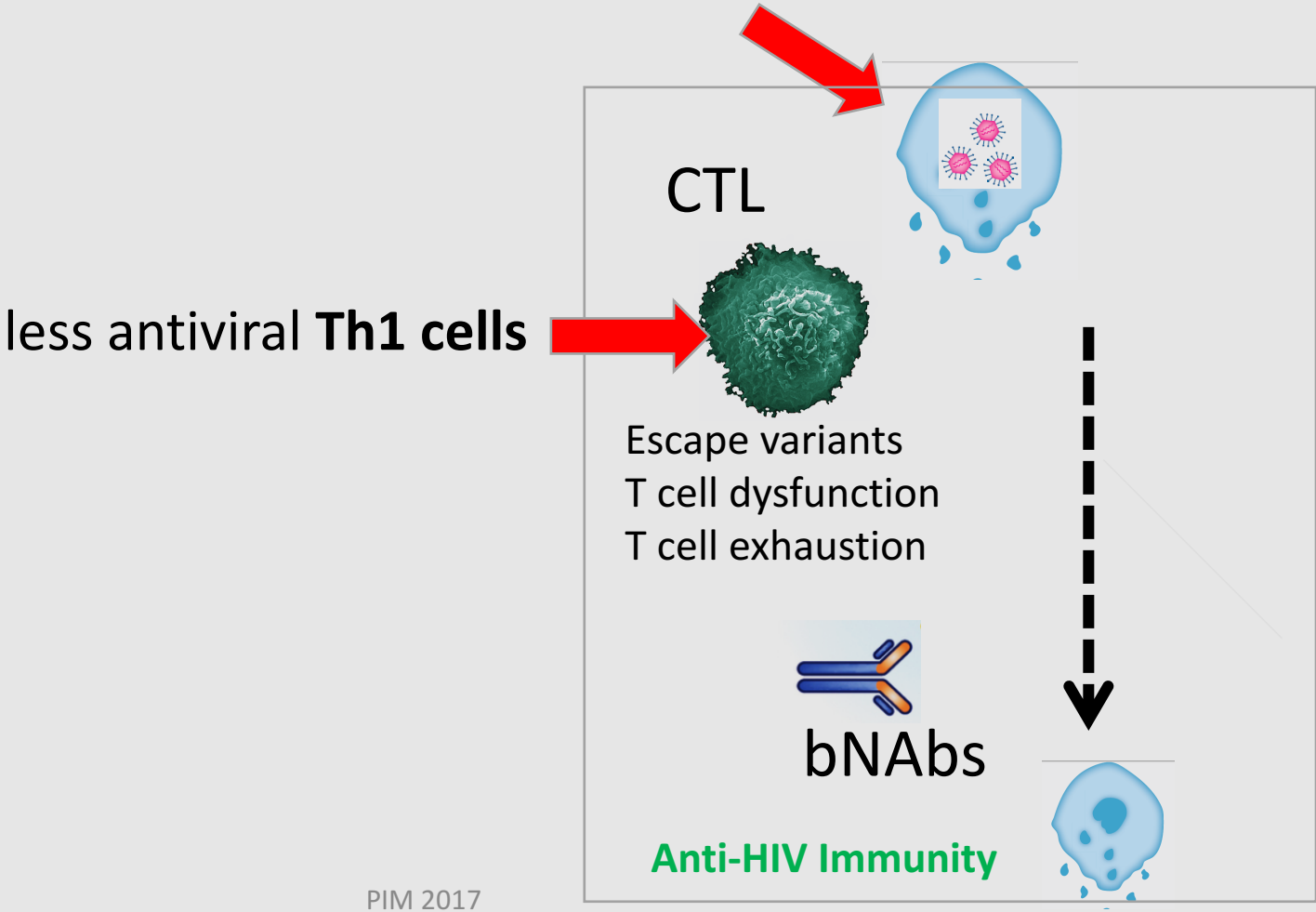
Mississippi baby



Persaud D et al., NEJM 2013

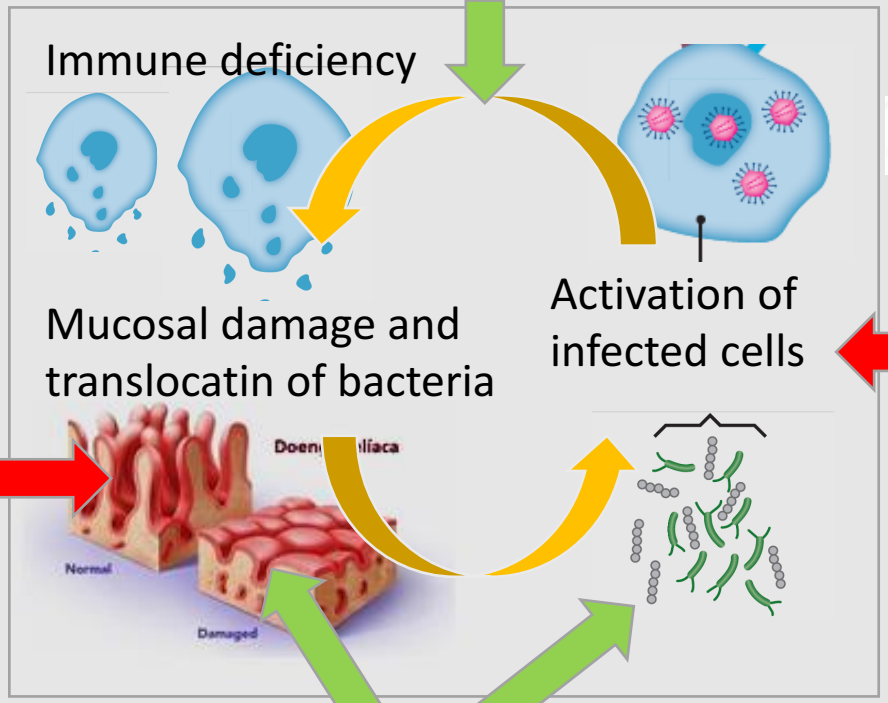
Pediatric specific points vs. Adults T cell responses

- Removal of HIV Antigen early: loss of memory response?



Pediatric specific points vs. Adults Immune activation/“Tolerogenics“

More **Treg cells** with very long half life 7 to 17yrs



Less activated T cells in blood, less CCR5+ T cells

Vaccinations, more infections

Decreased intestinal barrier in neonates

More **Th17 cells**

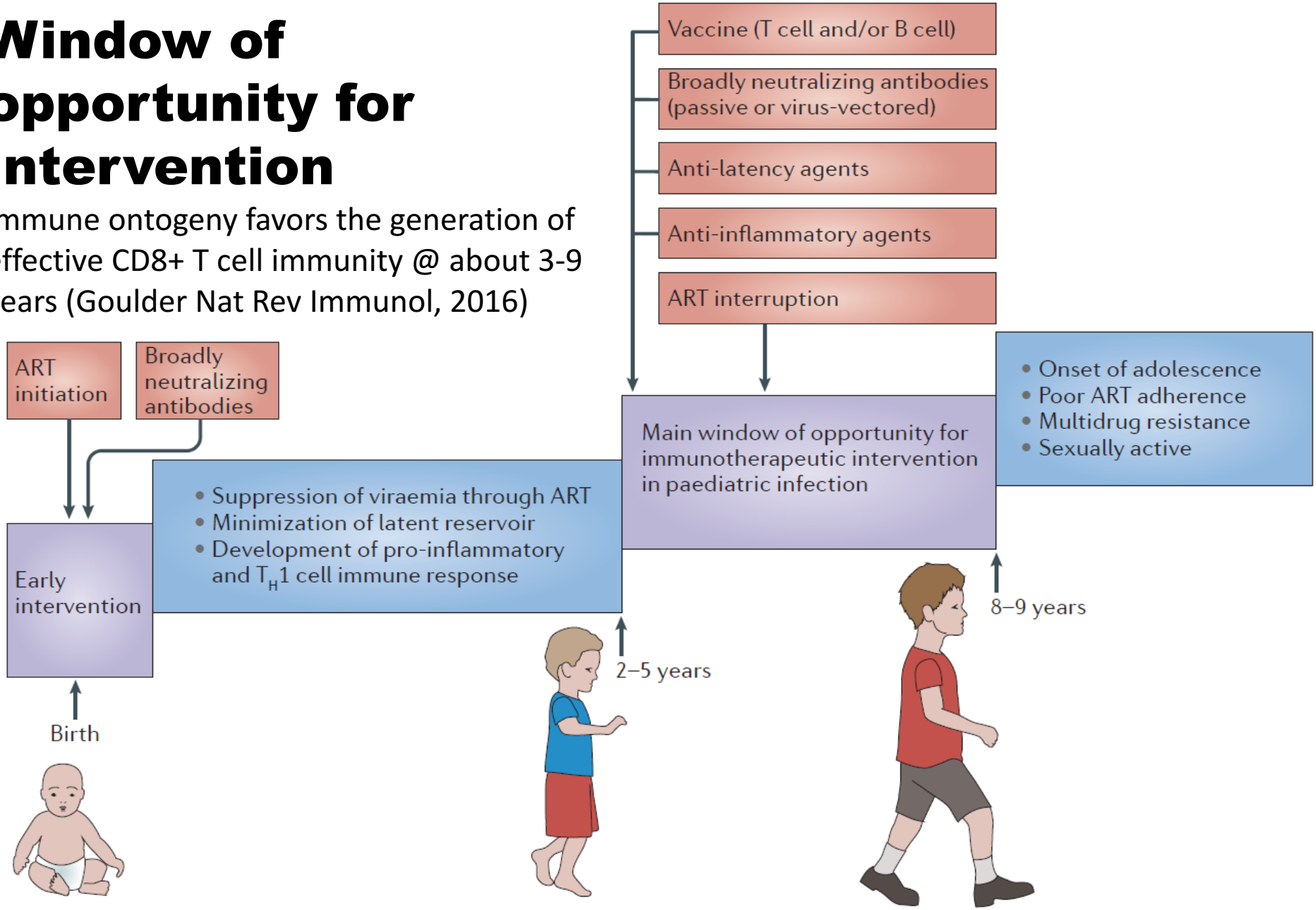
Conclusions III

- Tolerogenic environment perinatally (less inflammation) and prompt diagnosis in the neonate offer the chance to treat very efficiently
- Functional cure may be more easily achieved than in adults
- Eradication cure may only later be possible as antiviral Th1 responses need to mature up to 5-10 years of life

Thank you

Window of opportunity for intervention

Immune ontogeny favors the generation of effective CD8+ T cell immunity @ about 3-9 years (Goulder Nat Rev Immunol, 2016)



IMPAACT 2017

http://www.impaactnetwork.org/studies/

Phase I/II, multi-centre, open-label, non-comparative study

Oral cabotegravir (CAB), long-acting injectable cabotegravir (CAB LA), and long-acting injectable rilpivirine (RPV LA)

confirm dose, safety, tolerability, acceptability, PK