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Ending the HIV Epidemic:
What does 'HIV cure' have to do with it?

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Northwestern University

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Feinberg School of Medicine

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No conflicts to disclose

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Objectives Today

- Appreciate questions in research to sustain remission off-ART ("cure research") whose answers are relevant for potential impact on the "Ending the HIV Epidemic" Initiative.
- Understand different strategies for achieving sustained remission off-ART now being researched.
- Enhance critical thinking about significance for EHE of implementing remission strategies when reading the scientific literature or lay press

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Can research on HIV remission off-ART be relevant for EHE *in the future*?

NOT RELEVANT FOR EHE NOW

Requirements for relevance to ending the epidemic

- Remission strategy must be scalable to EHE jurisdictions…and everywhere else (globally)
- A major advantage would be if it allowed resources now committed to life-long ART to expand prevention and short-term ART prior to remission
- Potential benefit if remission decreased immune cell activation / systemic inflammation that persists on suppressive ART
  - Will that decrease infectious potential (eg, “blips” on ART)?
    - Possible if persistent HIV antigen is causal and removed
    - Not studied yet if cure decreases immune activation / imflammation
  - Will that decrease co-morbidities that are now biggest cause of morbidity/mortality on-ART (non-EHE benefit)?

The potential impact of a “curative intervention” for HIV: a modelling study

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

- Define key aspects of ‘target product profile’ for an HIV cure strategy so that it could impact the epidemic
- Current gaps in South Africa despite ART:
  - 14.3% of 15-24 yr old PLWH on ART (31% for 25-49 yo)
  - 1.5% annual HIV incidence in women 15-24 yr old, compared to men (0.5%) or older women (0.9%)
  - Young people projected to increase 80% by 2060
- Deterministic compartmental model of mature South African epidemic
  - Possible future LA PrEP and vaccine included
  - Impacts may differ if incidence lower

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Future epidemic scenarios

Cure introduced in either 2030 or 2040 (more impact starting earlier)

Table 1 Future HIV epidemic scenarios

	Pessimistic scenario	Neutral scenario	Optimistic scenario
Increase in condom coverage (2030 vs 2015)	No increase (85% efficacy)	5 percentage point increase (85% efficacy)	10 percentage point increase (85% efficacy)
ART Coverage	No increase in % PLWHA on ART beyond 2015 (70% efficacy)	By 2030, ART reaches 80–80-80 (80% efficacy)	By 2030, ART reaches 90–90-90 (92% efficacy)
VMMC	Decrease in % adult men circumcised (60% efficacy), reaches 35% by 2050	Increase in % adult men circumcised (60% efficacy), reaches 60% by 2050	Increase in % adult men circumcised (60% efficacy), reaches 70% by 2050
Oral PrEP	None available	Oral PrEP (40% efficacy) reaches 3% coverage by 2030	Oral PrEP (40% efficacy) reaches 10% coverage by 2030
Other Changes	None	None	Long-acting PrEP (75% efficacy) reaches 25% coverage by 2030. Vaccine (70% efficacy) coverage reaches 80% by 2050. Increase in percentage of adult men circumcised beyond 2015 (reaches 70% by 2050)

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

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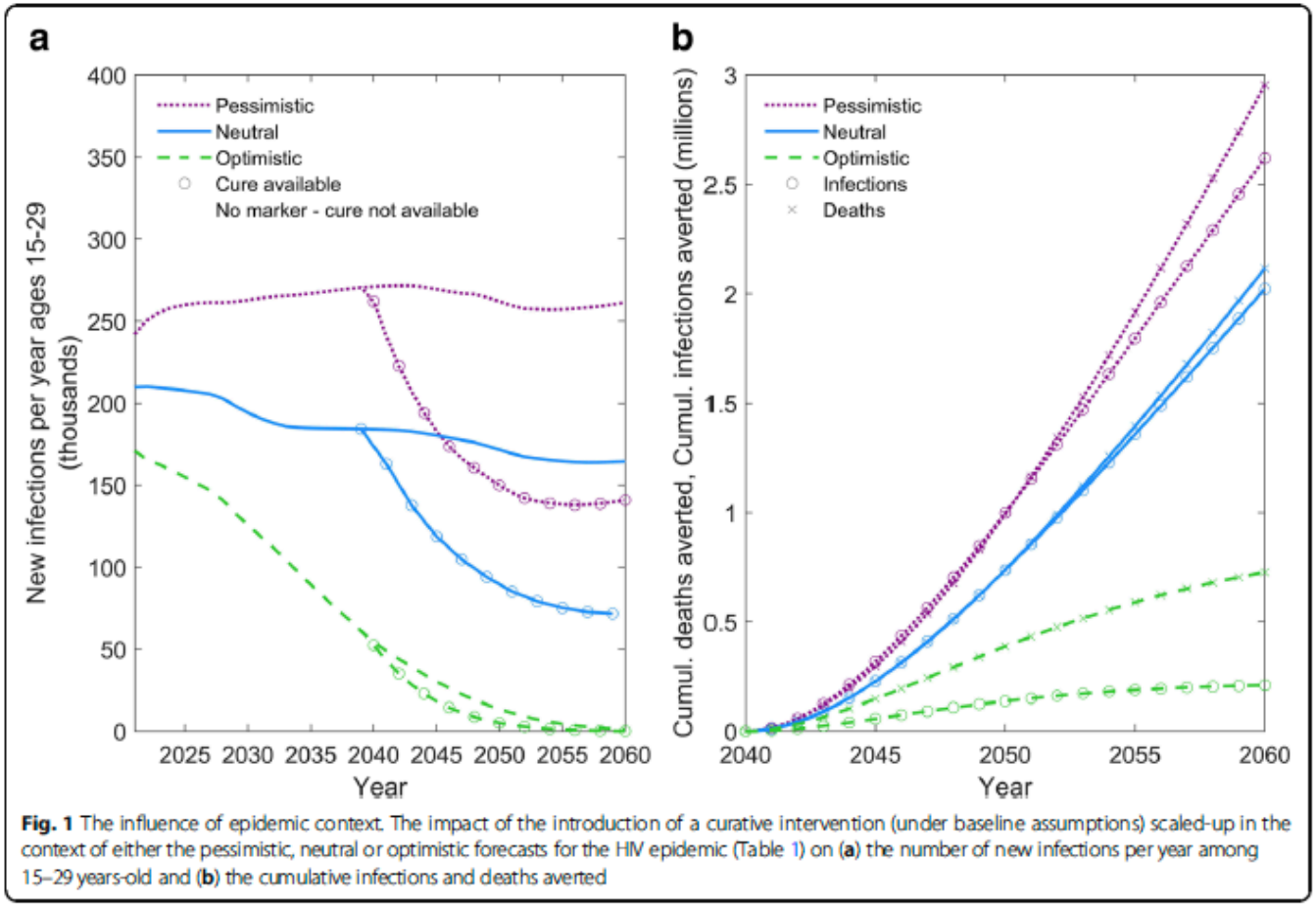

Fig. 1 The influence of epidemic context. The impact of the introduction of a curative intervention (under baseline assumptions) scaled-up in the context of either the pessimistic, neutral or optimistic forecasts for the HIV epidemic (Table 1) on (**a**) the number of new infections per year among 15–29 years-old and (**b**) the cumulative infections and deaths averted

Impact greater among younger PLWH – longer time to avert transmissions

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

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Impact of relapse –at 8 yrs vs at 20 yrs vs never

Earlier and more rapid scale-up of a cure has more impact than relapse – suggests starting imperfect intervention earlier is better than waiting for improvement

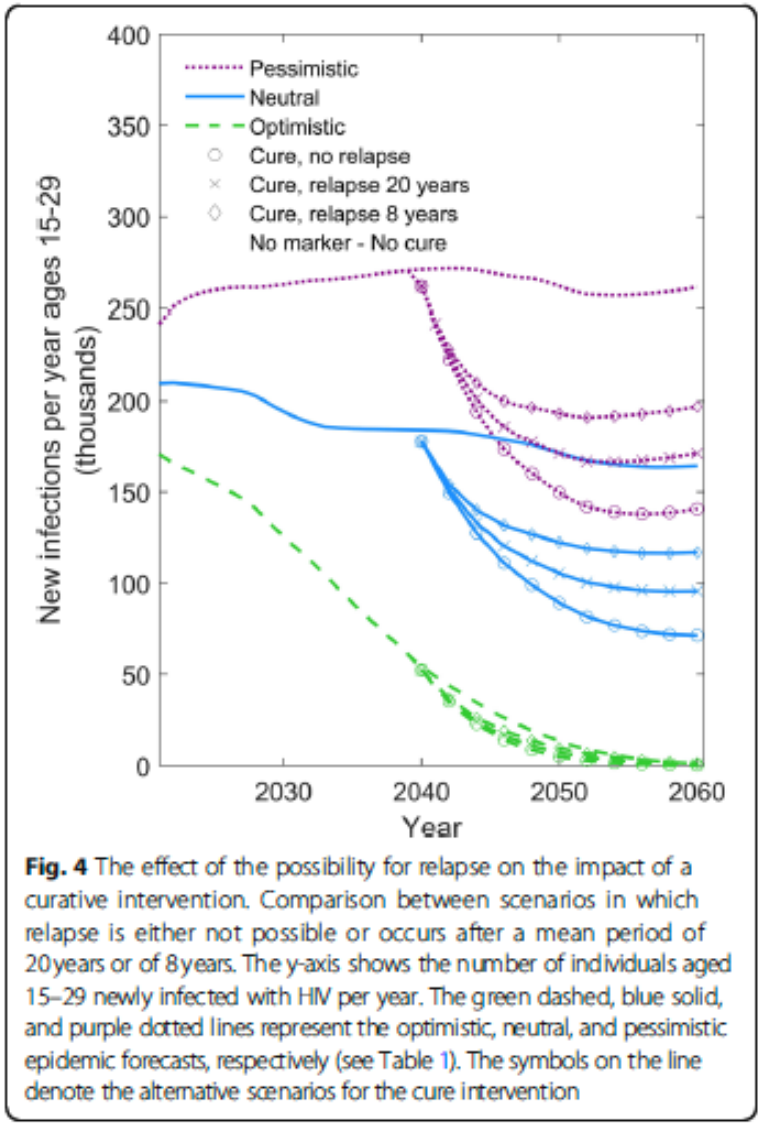

Fig. 4 The effect of the possibility for relapse on the impact of a curative intervention. Comparison between scenarios in which relapse is either not possible or occurs after a mean period of 20 years or of 8 years. The y-axis shows the number of individuals aged 15–29 newly infected with HIV per year. The green dashed, blue solid, and purple dotted lines represent the optimistic, neutral, and pessimistic epidemic forecasts, respectively (see Table 1). The symbols on the line denote the alternative scenarios for the cure intervention

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

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Cure strategy that prevents re-infection is KEY!

Allowing re-infection MUCH worse than a relapse

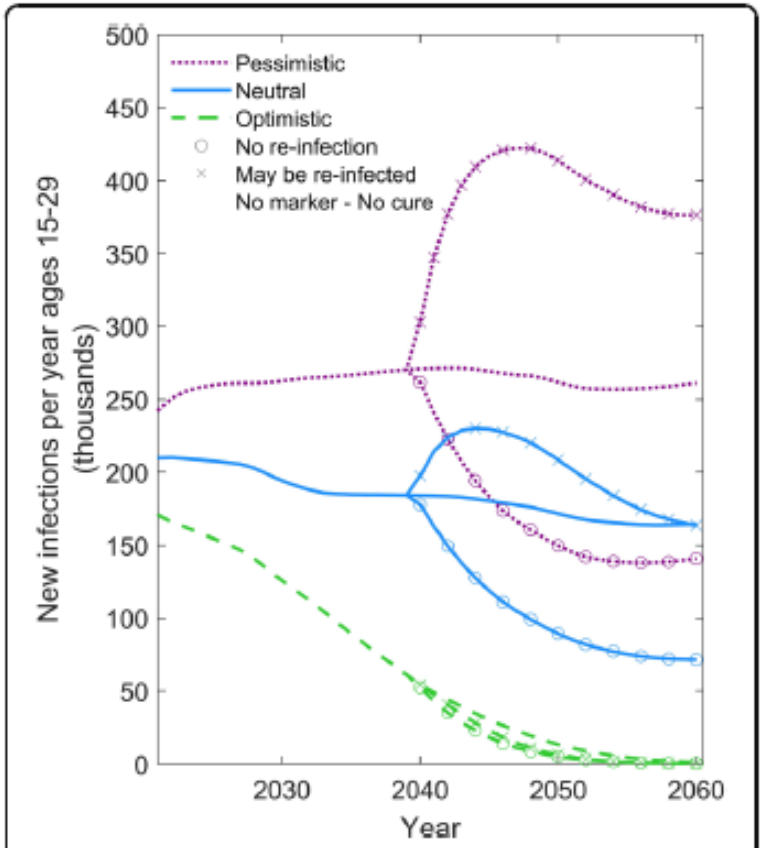

Fig. 3 Comparison of a curative intervention that prevents re-infection versus one that allows re-infection. Comparison of scenarios in which a curative intervention either allows for re-infection or prevents subsequent re-infection. The y-axis shows the number of individuals aged 15–29 newly infected with HIV per year. The green dashed, blue solid, and purple dotted lines represent the optimistic, neutral, and pessimistic epidemic forecasts, respectively (see Table 1). The symbols on the line denote the alternative scenarios for the cure intervention

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

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Target product profile for a cure

- Continue to suppress viremia after exposure to re-infection (eg, not allow re-infection)
- Lower risk of relapse (but some relapse OK)
- Best if it can be adopted by those not now starting ART or successfully suppressed long-term on ART
- Not modeled :
  - Potential additional benefit of decreasing persistent immune cell activation / systemic inflammation on suppressive ART

L. Beacroft and TB Hallett. *Global Health Research and Policy* 4:18; 2019

What do PLWH who are suppressed on-ART think?

Dube K, et al. The Dose Response: perceptions of PLWH in the US on alternatives to oral daily ART. *AIDS Res Hum Retro.* In press, 2019

- 55 of 282 (24%) willing to switch to a hypothetical (undefined) ART-free remission strategy
  - Second to other choices:
    - Long acting systemic ART (inject or implant; 125 of 282 - 44%)
    - Not switching from daily oral ART (20 of 282 - 7%)
- Most desirable attribute of a remission strategy was complete elimination of HIV from the body
  - Consistent w 2 earlier focus group papers where risk of rebound limited advantage of functional cure over daily ART
  - Fear of decreased cognition biggest deterrent to cure research participation – not cancer
  - Altruism was biggest incentive
- If long-acting systemic ART has a "tail", enrollment in analytical treatment interruption research may become difficult

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Strategies for sustaining HIV remission off-ART

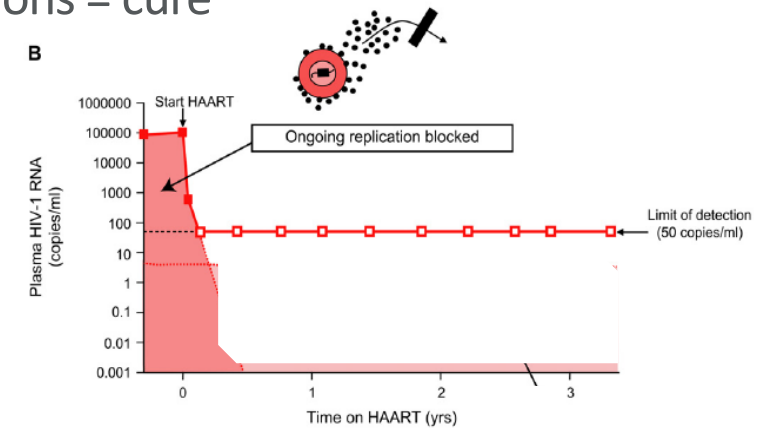
Dogma and Controversy

Steps Forward…and Back

- Antiretroviral therapy (ART) can cure (Wrong)
- HIV persistence / latency is life-long – cure impossible (Wrong)
- Cure with possibly incomplete eradication (n=1) rekindles research
  - CCR5-deficient allogeneic stem cell transplant, now 3 successes reported in Hiv and cancer patients
- Other strategies than transplant
  - ‘Shock and Kill’ / ‘Latency reversal’
  - ‘Post-treatment control’ with early ART
  - ‘Block and Lock’
  - Gene editing (CRISPR most recently) – to make CCR5 or HIV defective
  - Immune-based strategies, BnABs now most promising / combo
  - Newer ideas in development based on learnings / problems

1997: new ‘HAART’ alone can cure

- After starting ‘HAART’, rate of viremia decay reflects rate of decay of virus-producing cells (based on viral load assay lower limit <200c/ml)
  - “First phase” - <1 day half life – infected activated T cells
  - “Second phase” - 2 week half-life – infected macrophages
  - Perelson and Ho – cells infected pre-ART die after a few years of suppression of new infections = cure



From Shen and Siliciano 2008

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But…

- Viremia rebounds 14-21 days after ART stops
- Siliciano identified a "3rd phase of viremia decay" (after viral load lower limit decreased)
  - A "viral outgrowth assay" recovers replication competent HIV from patient sorted resting T cells that were activated *ex vivo* with PHA or anti-CD3/28 Ab
  - Low level – about 1 reactivatable HIV provirus per million resting T cells
  - No decrease in quantity of "reactivatable" HIV over many decades of suppressive ART
- Other reservoirs possible (CNS, myeloid cells, ?kidney epithelium)

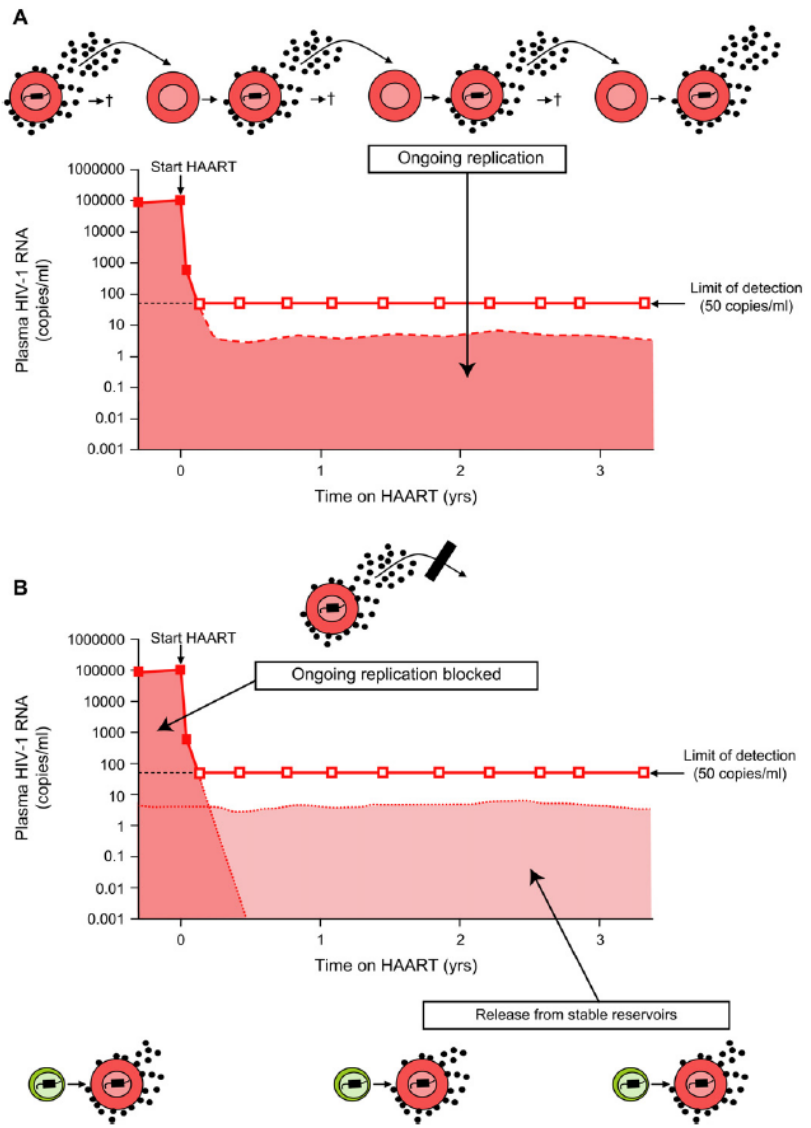
New Picture:

From Shen and Siliciano 2008

>70 years estimated for a pool of 1 million latently infected resting cells to decay

SO…NEVER ERADICATE

Consensus: stable reservoir of HIV
Controversy: does HIV replicate on-ART?



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DOGMA: HIV persists in resting memory T cells as a "silenced provirus" due to:

- 1) deleterious mutations in the viral genome (some of which could be repaired by recombination if more than one virus integrates in the same cell)
- 2) transcriptional interference
- 3) changes in chromatin structure (heterochromatin)
- 4) epigenetic silencing (such as increased DNA methylation, histone deacetylation)
- 5) presence of negative transcription factors
- 6) absence of positive transcription factors
- 7) problems with HIV RNA processing and transport

Cary DC et al 2016

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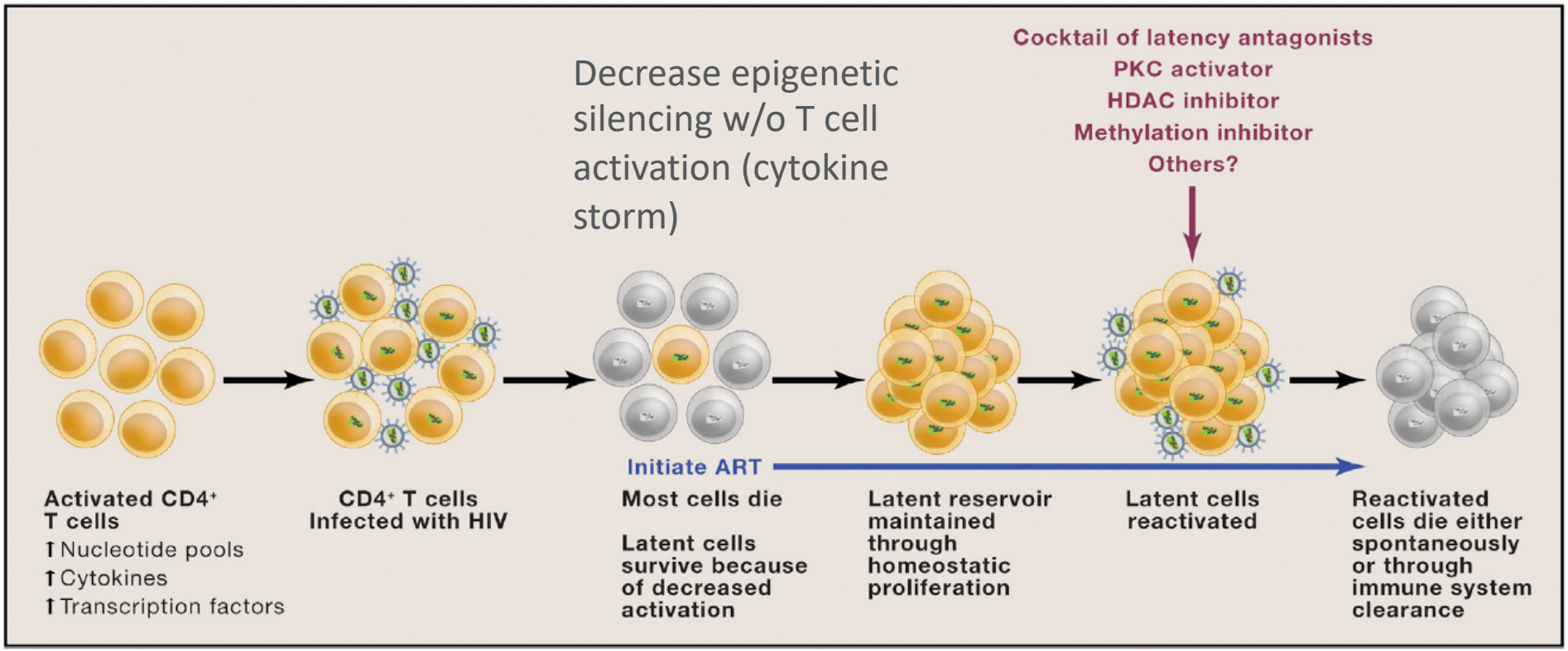
"Shock and Kill" Strategy

- Assumes long-lived reservoir cells and NO HIV replication



From Ruelas and Greene, Cell 2013

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Latency Reversing Agents (LRAs)

- HDACi (vorinostat, romidepsin) increase transcription from many 'silenced' human genes (not only HIV)
  - Reactivate only a subset of silenced HIV proviruses activated by TCR signals
  - Increased cellular HIV RNA seen, but not clear if virus released or if it's infectious
  - Cells with reactivated provirus do not die from cytopathic effect ex vivo
    - Return to rest with latent provirus unless CTL activity can be augmented to kill them when expressing HIV antigens
    - Most proviruses have CTL escape mutations
    - Lymphoid sites CTL cannot access
    - Even when effective CTL get to the cells reactivating HIV, they resist killing (immune checkpoint block killing)

New immune approaches to combine with LRAs

- Rhesus CMV vector expressing HIV antigens (majority of SIV infected macaques control viremia)
- Broadly neutralizing antibodies (passive immunization)
- Even maximal T cell activation reactivates only a subset of HIV proviruses
  - Repeated rounds of maximal activation needed?
  - Cumulative cancer risk

Other shortcomings of 'Shock and Kill'

- Will not prevent another infection
- Relapse risk may remain if some viruses 'deeply latent' but replication-competent

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Opposite approach to reactivation: Block and Lock-in Latency

S. Valente

- Again, based on dogma that all persistent virus is transcriptionally latent
  - Evidence of ongoing virus replication and infected cell proliferation (presented later) raises questions
  - Also cannot prevent re-infection and relapse will remain possible

Timothy Ray Brown (“The Berlin Patient”)
SCT X2: HIV cure with complications
Appropriate for PLWH & some cancers
NOT SCALABLE

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Now accepted as a cure of HIV – but only R5-tropic HIV

- Inspired NIH to prioritize HIV cure research yrs ago

- SCT replacing immune system with cells that HIV cannot enter because they have a homozygous defect in CCR5 co-receptor for HIV
  - Lack of HIV-susceptible cells
  - 'Conditioning'/GVHD killed all pre-SCT immune cells
  - Some X4 tropic virus detected / variable HIV RNA
  - Modeling suggests >10 years enough for possible stochastic reactivation of any remaining provirus
    - Now at >10 years
    - Reportedly on PrEP : CXCR4-tropic virus infection possible

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‘London Patient’ cured of AML and likely HIV (>18 mos)

Gupta RK, et al. HIV-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation. Nature. 2019 Apr;568(7751):244-248.

- Confirms role in remission of CCR5 delta 32 mutation disabling the HIV co-entry receptor in allogenic, engrafted immune cells
  - Prevents viremia rebound
- Less aggressive conditioning / no irradiation / single SCT
- No HIV RNA or reactivatable virus to date
- Lost anti-HIV immune responses
- Same team reported a ‘Dusseldorf patient’ with >1yr off-ART after allogeneic SCT with CCR5 defective allogeneic cells

“Boston patients”: SCT with NORMAL CCR5

Henrich TJ, et al. Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. Ann Intern Med. 2014;161(5):319-27.

- Sustained remission – but virus virus rebounded many months later (not 2-3 weeks)
  - WHY?
- Allogeneic SCT for cancer – but NO CCR5 defect, so HIV could enter new immune cells normally
- Maintained ART to block HIV spread to new immune cells – but then stopped when VOA showed ‘undetectable’ latent reservoir
- Timing of rebound consistent with smaller reservoir – just below level of detection of assays

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Other allogeneic SCTs for cancer & HIV with normal CCR5 (hard to find CCR5 defective donors)

Salgado M, et al. Mechanisms That Contribute to a Profound Reduction of the HIV-1 Reservoir After Allogeneic Stem Cell Transplant. Ann Intern Med. 2018 Nov 20;169(10):674-683.
D'Aquila R. Learning About "Known Unknowns" and "Unknown Unknowns" to Cure HIV. Ann Intern Med. 2018 Nov 20;169(10):719-720.

- Evidence that 'Graft vs HIV' (clinical or subclinical graft vs host disease) effect contributes to marked reduction in amount of persistent HIV detected
- IciSTEM team will add BnAB combination at time of stopping ART to see if remission can be prolonged
  - Could also learn what triggers reactivation and when??
  - BnAB questions
    - will repeated dosing be needed or can a gene therapy vector deliver long term?
    - Will anti-'drug' antibodies develop?
    - Can an escape mutant reinfect?

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Gene Editing of autologous cells – CRISPR/Cas9

Xu L, et al. CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia. N Engl J Med. 2019 Sep 26;381(13):1240-1247
June CH. Emerging Use of CRISPR Technology - Chasing the Elusive HIV Cure. N Engl J Med. 2019 Sep 26;381(13):1281-1283.

- Hard to find HLA compatible, CCR5-defective allogeneic stem cell donors
- Editing autologous cells can introduce the defect in CCR5
  - Need multiple edits to prevent HIV from escaping by mutation
- HIV viremia rebounded – only 5 to 8% of cells had defect in CCR5
  - No immune reaction to bacterial enzyme (Cas9)
  - Off target effects could not be well evaluated given limited number of edited cells
- Important context for a humanized mouse study of CRISPR/Cas9 to inactivate HIV
  - Dash PK, et al. Sequential LASER ART and CRISPR Treatments Eliminate HIV-1 in a Subset of Infected Humanized Mice. Nat Commun. 2019;10(1):2753.

Sustained remission after early ART

- Post-treatment control (sustained remissions)
  - VISCONTI – 13 adults
  - Few others
  - None had pre-ART viral load tested
  - One 'Mississippi baby' – ART at 30 hours, then stopped at 15 months with no viremia for >2 years
- Lack of any delay in viremia rebound in adult subjects suppressed VERY early (in Fiebig 1)
  - Colby et al. 2018 – RV411
  - Suggests that in adults those with 'post-treatment' may have been spontaneous controllers

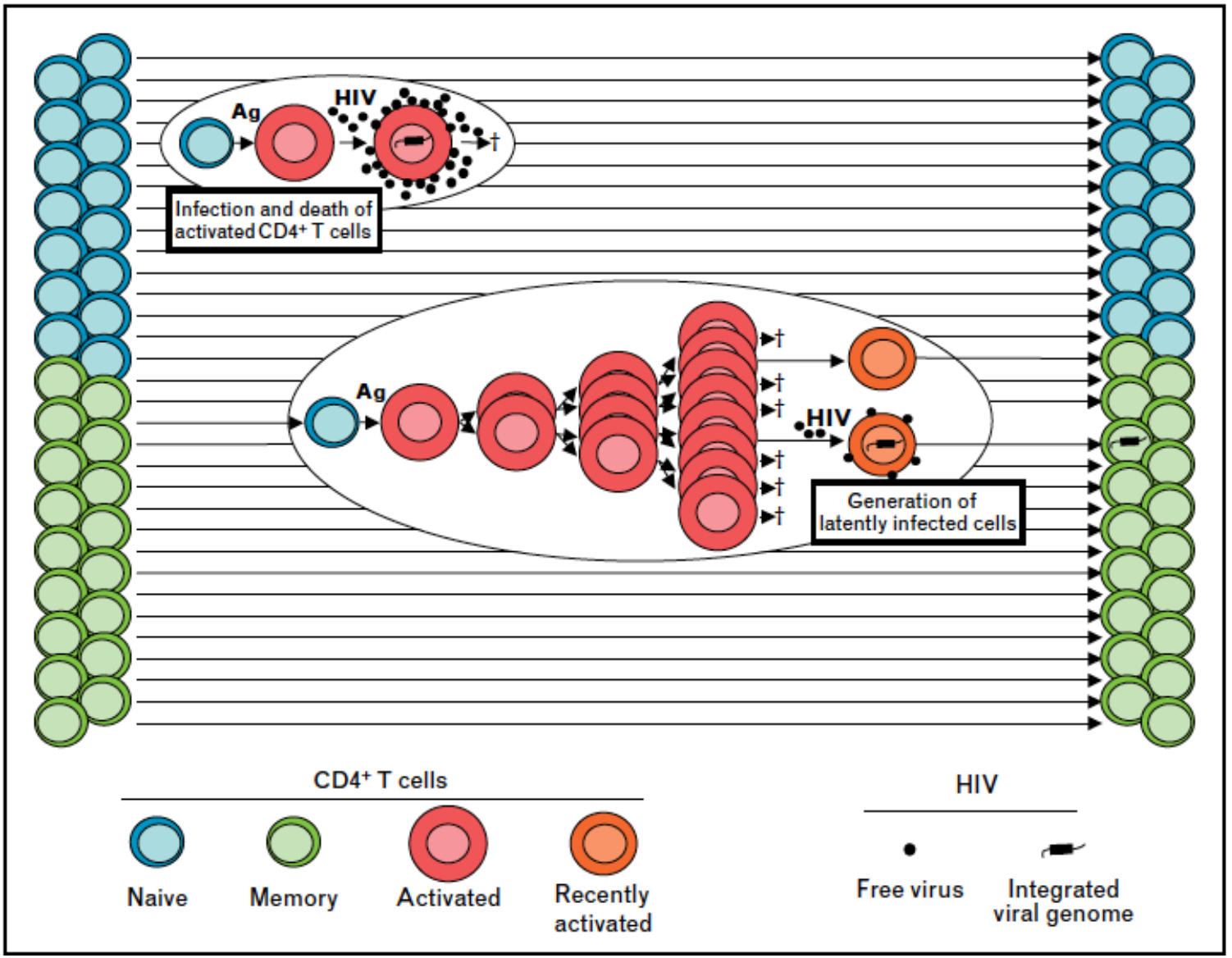
Revisiting dogmas with controversial new data - I

- Does HIV replication continue at a low level in some tissues during ART (‘drug sanctuaries, perhaps) to replenish the reservoir?
  - Highly controversial studies of excised lymph nodes (Lorenzo, et al)
  - “Immuno-PET” imaging using radio-labeled anti-SIV envelope antibody identifies antigen expression persisting during viremia-suppressing ART in macaques (Tom Hope and Francois Villinger)

Revisiting dogmas with controversial new data-II

- Does the ‘latent reservoir’ decay more quickly - and maybe not persist lifelong on suppressive ART?
  - 3 PLWH studied by O’Doherty’s group suggest replication competent viruses decrease, but proliferation of cells with replication-incompetent HIV outcompetes the decrease (Pinzone MR, at al. Nat Commun. 2019;10(1):728)
- Sequences of persistent low level viremia on ART revealed identical HIV genomes and later this was learned to be caused by release from a ‘clonal proliferation’ of one cell harboring a single provirus
  - HIV can be integrated into small number of genes involved in cell proliferation
  - Recently, Mellors group identified that “blips” were due to a clone expanding by cell proliferation and NCI group found infected cell proliferation maintained persistence in lymph nodes

DOGMA: Latency is established when T cells Infected while activated return to rest before dying.



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Direct infection of resting memory T cells also possible

- O'Doherty, Lewin and others

- Chemokines (CCL19, CXCL9, CXCL10, CCL20) facilitate resting cell infection, without causing T cell proliferation

Revisiting dogmas with controversial new data-III

- What T cell types comprise the latent reservoir?
- Dogma: Central memory and effector memory T cells in blood (Tcm, Tem) (Chomont)
- More recent: Th17, Tfh
  - Tfh in follicles may continually produce virions
- Which tissues contribute to viremia rebound off-ART? - Blood, LN, gut?
- De Scheerder MA, et al. HIV Rebound Is Predominantly Fueled by Genetically Identical Viral Expansions from Diverse Reservoirs. Cell Host Microbe. 2019;26(3):347-358.e7.
- Most recent paper addressed which tissues and cell types contribute to, and role of cell proliferation, in viremia rebound after stopping ART
- 11 participants in analytical treatment interruption (ATI)
  - No primary tissue source or cell type (naïve, Teff as well as Tcm and Tem)
  - Cell clone proliferation can contribute greatly
  - HUGE variability from one person to another

Reservoir established at time of ART initiation

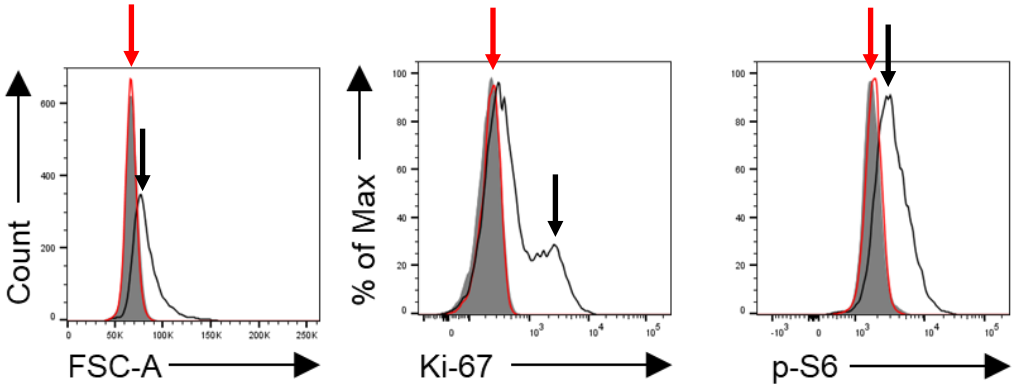
Abrahams M-R, et al. The replication-competent HIV-1 latent reservoir is established near the time of therapy initiation. Sci Trans. Med 2019;11

- 9 women on ART from CAPRISA II underwent ATI
- 71% had rebounding plasma virus sequences most similar to viruses present near time ART started
  - Not related to sequences from earlier in infection
- Conclude that ART alters host environment to allow formation or stabilization of most of long-lived HIV reservoir
- Hypothesis:
  - IL-7 receptor (IL-7R)-positive memory CD4 T cells are depleted during untreated HIV infection by infection and bystander loss
  - IL-7/IL-7R signaling needed for transition of Teff to memory T cells and their homeostatic maintenance over a long time
  - With ART start, frequency of IL-7R-positive memory CD4 cells increases and more infected effector cells transition to long-lived memory
  - Suggests that stopping IL-7/IL-7R signaling or proliferation of those cells when ART starts may block establishment of latent reservoir

IL-15/7 induces mTOR activity and exhaustion markers associated with HIV persistence

IL-15 induces CD4 T cell growth and proliferation in HIV target cells via mTOR

- IL-15 treated HIV target CD4 T cells (black arrows) display increases in cell size (FSC-A), proliferation (Ki-67), and mTOR activity (p-S6)
- Treatment of IL-15-exposed CD4 T cells (red arrows) with a highly specific mTOR inhibitor blocks these responses

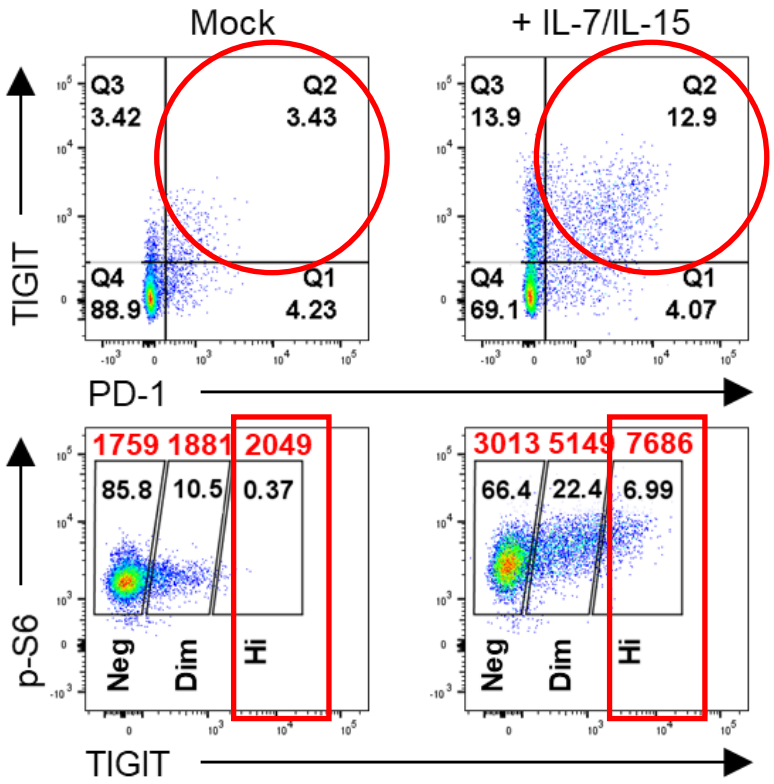


Taylor et al, 2018 (*AIDS*)

IL-15/IL-7 induces exhaustion markers associated with HIV persistence

- IL-15/IL-7 treatment induces expression of immune exhaustion markers PD-1 and TIGIT, which identify cell populations known to be enriched for latent and actively replicating HIV in patients

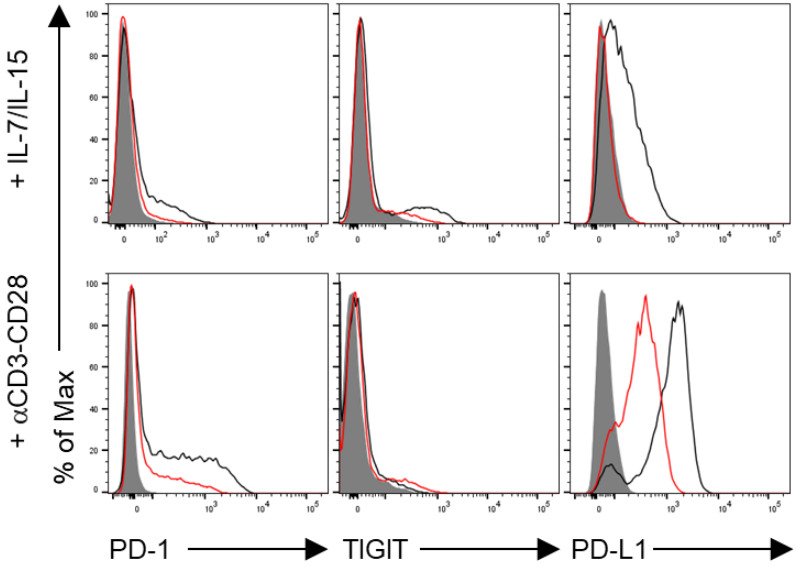
- Exhaustion marker expression directly correlates with mTOR activity in IL-7/IL-15-treated CD4 T cells.



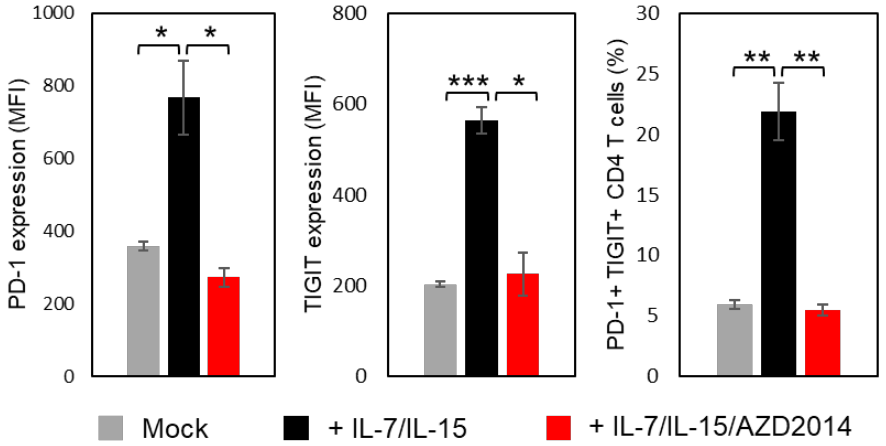
Taylor et al, 2018 (*AIDS*)

IL-15/IL-7 mediates effects via mTOR activity

Blood CD4 T cells



Colon mucosal CD4 T cells



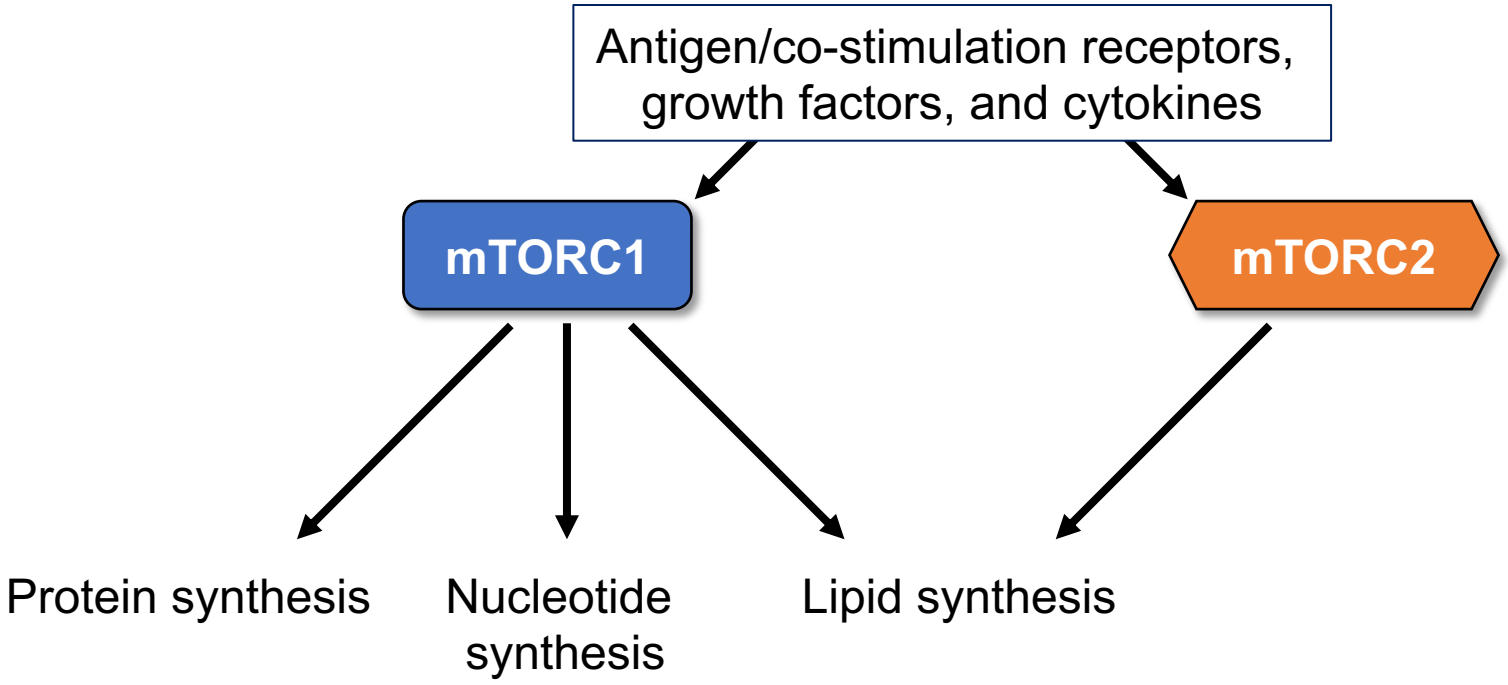
- **Conclusion: IL-7/IL-15 stimulation induces T cell exhaustion markers via mTOR in both blood and mucosal tissue.**

Taylor et al, 2018 (*AIDS*)

Summary

- CD4 T cell mTOR activity (a driver of HIV infection, persistence, and T cell exhaustion) is increased by higher IL-15 (and IL-15/7) levels
- mTORi blocks induction of T cell exhaustion markers in presence of IL-15/7

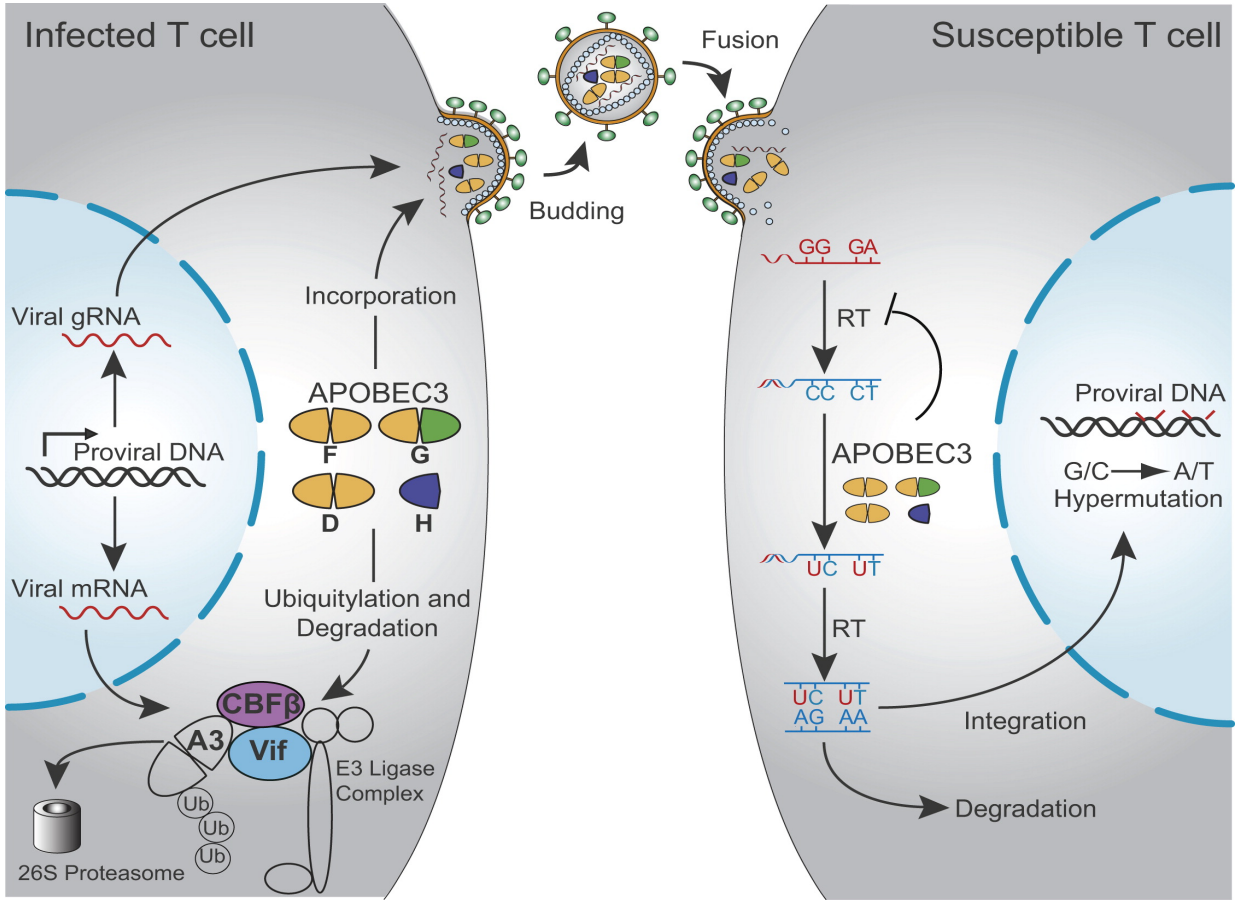
Mechanistic target of rapamycin (mTOR) governs anabolic metabolism in response to environmental signals



Summary

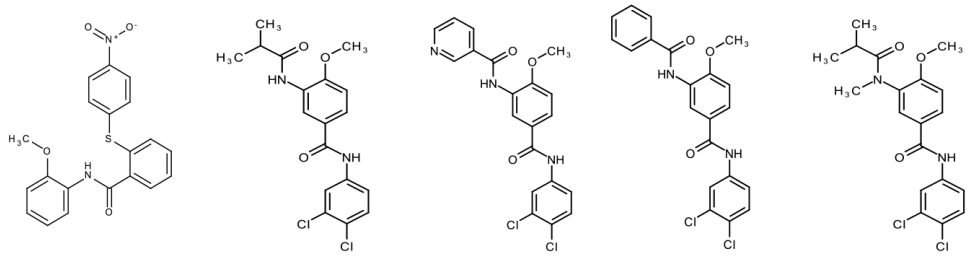
- mTOR drives CD4 T cell activation-induced expansion of metabolites that fuel HIV replication
  - mTOR regulates multiple enzymes that make all dNTPs for RT and acetyl-CoA for cytoplasmic trafficking and nuclear import
  - Catalytic mTOR inhibitors (now in development for cancer) block all this
  - Can they block IL7/15 function needed to establish HIV reservoir, and add anti-HIV effect, if overlapped with ART start?
  - Will catalytic mTOR inhibitors block cytokine-driven infected cell clonal proliferation at time of viremia rebound when ART stops?
- How block re-infection?
  - Maybe BnAB, CRIPSR editing of autologous cells (as well as CCR5 defective allogeneic SCT)

Can we leverage APOBEC3 Intrinsic Immunity?



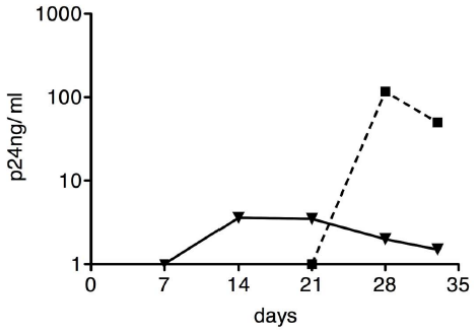
Virology, Volumes 479–480, 2015, 131–145

Chemical Structures of NU compounds that boost A3s



RN-18 NU52 NU307 NU309 NU611

Tools to discover how A3s are regulated in the cell and whether they can stay high and protect against Vif+ HIV after a remission strategy



Naturally low pre-infect A3

Naturally high pre-infect A3

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