

Summary for the community

- **Key question asked:** What is the relationship between viruses in the latent reservoir and viruses that cause viral rebound when ART is interrupted.
- **Key finding:** Only a subset of viruses in the reservoir can cause rebound. The rest are controlled by the immune response.
- **How is this important for an HIV cure?** We need to find a way to control the rest of the viruses in the reservoir.

SUMMARY FOR COMMUNITY

- **Key Question:** Can we identify non-invasive plasma biomarkers of duration and probability of viral remission after treatment interruption?
- **Key Finding:** Using advanced technologies and machine learning algorithms, we identified plasma non-invasive pre analytical treatment interruption (ATI) biomarkers that predict duration (by 74 to 76%) and probability (by 97.5%) of viral remission upon ART cessation.
- **Why important and How related to Cure?** These biomarkers could improve the safety of ATIs during HIV cure-oriented clinical trials and also can serve as windows into the mechanisms that contribute to post-ART HIV control.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **Can T cells be engineered to control HIV?**
- **What was the key finding / take-home message?**
 - ❖ **By putting two chimeric antigen receptor (CAR) into a single T cell we get the best qualities of each.**
 - ❖ **Protest the current administration decision to ban the use of fetal tissue and encourage the new administration to reverse this ban.**
- **How is this important for an HIV cure?**
 - ❖ **Engineered T cells will likely play an important role in a HIV cure strategy as they can be used to reduce the reservoir (eradication) as well as surveying the body looking for re-awakened HIV infected cells (functional cure).**

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Can the combination of vaccines and antibodies lead to virus remission or eradication in an animal model?
- **What was the key finding / take-home message?**
 - ❖ In a study in infected monkeys, we showed that vaccines led to reduced virus replication and that antibodies delayed viral rebound when antiretroviral drugs were stopped. The combination of vaccines and antibodies led to both effects.
- **How is this important for an HIV cure?**
 - ❖ These findings suggest that vaccines and antibodies are promising strategies that should be studied further for an HIV cure.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ What can we learn by evaluating multiple clinical trials with analytic treatment interruption (ATI) in Thailand together as a larger group?
- **What was the key finding / take-home message?**
 - ❖ It is statistically valid to combine data from these smaller trials together. This larger group analysis has shown us that certain clinical measurements predict who may have a longer time without high levels of HIV in the blood after stopping their antiretroviral medication
- **How is this important for an HIV cure?**
 - ❖ By understanding predictive measures of time to “viral rebound” after stopping medication, in the future we may be able to more reliably evaluate the effectiveness new therapies for cure without asking volunteers to stop their antiretroviral medications

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ The HIV reservoirs consists of different clones of cells with a “live” (intact) copy of HIV in the cells DNA. What are the forces that promote clonal expansion and persistence of the HIV reservoir?
- **What was the key finding / take-home message?**
 - ❖ The location in the cells DNA where the HIV sits can be important in promoting clone formation but growth of T-cell clones in response to common viruses like cytomegalovirus is probably more important.
- **How is this important for an HIV cure?**
 - ❖ Understanding the factors that drive the clonal expansion of infected cells is critical for designing therapies to block formation and persistence of the reservoir

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Is 'hiding' from the immune system (latency) the full story of how HIV persists? or are cells that harbor HIV intrinsically hard to kill?
- **What was the key finding / take-home message?**
 - ❖ Cells harboring the HIV reservoir are hard to kill, even when they are seen by cytotoxic T-lymphocytes (CTL)
 - ❖ So far, we have discovered three mechanisms of CTL resistance, with many more being explored
- **How is this important for an HIV cure?**
 - ❖ Most approaches to cure have focused on exposing hidden virus to the immune system
 - ❖ Our work suggest a complementary or alternative approach or making infected cells more sensitive to killing by CTL (ex. with therapeutics)

Why should the Community BELIEVE?



Question: Why should we care about naive T cells. Isn't the viral reservoir in memory T cells?

Key finding: Naive T cells have been considered inconsequential to HIV because they have lower levels of HIV DNA, but sequencing of this DNA uncovered their central role in the persistence of replication-competent HIV. Only the replication-competent HIV can cause disease.

Take home message: Perhaps we have been looking in the wrong place.

Importance for HIV Cure: Naive T cells provide an excellent place for HIV to hide because they are longer lived and probably less susceptible to being eliminated by our immune system. They therefore represent a unique hurdle to HIV eradication and should no longer be ignored.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ How does treatment with IL-15 (N-803) and bNAbs impact the SIV reservoir in ART-suppressed non-human primates?
 - ❖ Does this combination therapy modify the immune system in such a model?
- **What was the key finding / take-home message?**
 - ❖ The combination of N-803 and bNAbs was safe in all treated animals.
 - ❖ We observed enhanced control of viremia after rebound in combination-treated monkeys.
 - ❖ We did not see large changes in the viral reservoir in tissues or blood.
 - ❖ Control of rebound viremia appears to be CD8+ T cell mediated.
- **How is this important for an HIV cure?**
 - ❖ Combination treatments that enhance T cell immunity may assist immune control of rebound virus in the absence of antiretroviral therapy.

SUMMARY FOR COMMUNITY

Neutralizing antibodies block HIV from infecting a cell

Non-neutralizing antibodies stick to HIV but do not prevent it from infecting

What key question was asked?

- Do combinations of neutralizing and non-neutralizing antibodies or antibody-like molecules called DARTs improve killing of cells infected with HIV-1 or a hybrid HIV/SIV virus?

What was the key finding / take-home message?

- Combination of three antibodies were the most potent at killing HIV-infected cells
- Addition of the non-neutralizing A32 antibody significantly improved killing
- A combination of three Ab-based molecules improved killing of SHIV-infected cells

How is this important for an HIV cure?

- Properly combining antibodies with different properties may be important to effectively and completely eliminate the viral reservoir

Summary for the Community

What key questions were asked?

- What is the relationship of the intact proviral DNA assay (IPDA) and the quantitative viral outgrowth assay (QVOA) HIV reservoir measurements over time in participants on ART?

What were the key findings/take-home message?

- IPDA proviral frequencies tracked over time with QVOA measurements in most participants
- Intact proviruses decrease over time similarly to QVOA virus but defective proviruses appear to be much more stable over time

How is this important for an HIV cure?

- This study help support the idea that the IPDA is an important tool to use to determine if there are changes in the replication-competent HIV reservoir during clinical trials seeking to cure HIV infection

SUMMARY FOR COMMUNITY

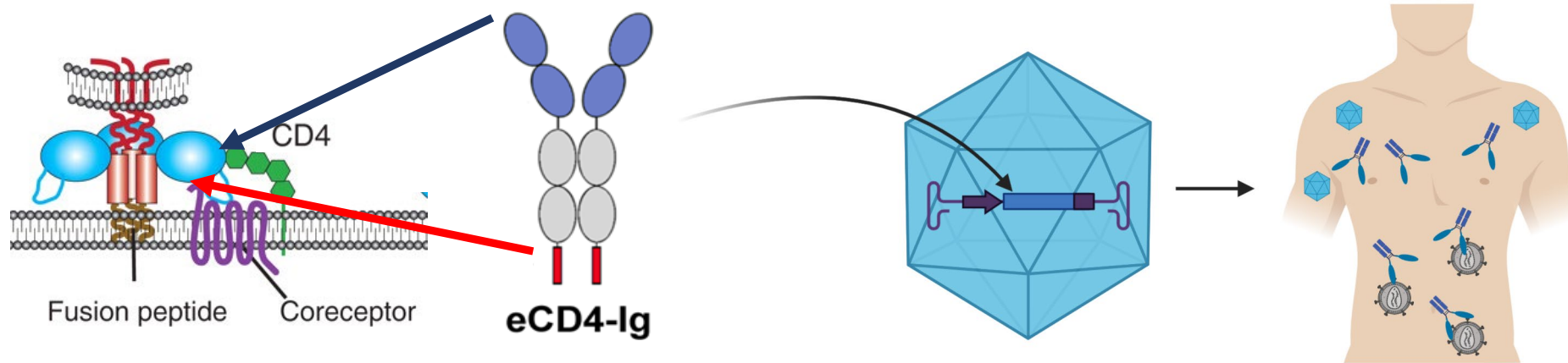
- **What key question was asked?**
 - ❖ Can we target signaling pathways in CD4+ T cells to reverse latency?
 - ❖ How does removal of CD8+ T cells impact latency reversal?
- **What was the key finding / take-home message?**
 - ❖ Activation of the non-canonical NF- κ B signaling pathway in CD4+ T cells reversed latency in two preclinical animal models and in cells from volunteers living with HIV.
 - ❖ Removal of CD8+ T cells enhanced the latency reversal potential of two agents (AZD5582 and N-803) targeting different signaling pathways.
 - ❖ Latency reversal was safe in both experiments and animal models.
- **How is this important for an HIV cure?**
 - ❖ These results demonstrate a two strategies for an effective “kick” that can be tested in combination with clearance approaches to reduce or eliminate persistent reservoirs.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ CAR T cells have revolutionized the treatment of cancer. Can they be similarly applied for HIV remission?
- **What was the key finding / take-home message?**
 - ❖ CAR T cells for HIV work extremely well, but need more “helpers” than do CAR T cells for cancer.
- **How is this important for an HIV cure?**
 - ❖ Our goal is stable HIV remission in the absence of ART for all people living with HIV. CAR T cells have allowed us to put a foot in the door. Our focus now is to identify the best helpers, and simplify the process so that it can be applied anywhere in the world.

Community Summary

- Key Question: Can eCD4-Ig (antibody-like, HIV entry inhibitor) delivered by adeno-associated virus (AAV) vectors and expressed by muscle cells suppress an ongoing infection in monkeys in the absence of daily ART?



- Key Result: When monkey muscle cells injected with AAV vectors make eCD4-Ig, monkeys have their virus suppressed for over 2 years after stopping daily antiretroviral therapy.
- Importance to an HIV Cure: AAV vectors delivering HIV inhibitors could one day replace daily cART and suppress viremia.
 - Excitement: Could become “one-shot” treatment for controlling virus without other drugs.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **Can we use genetic engineering to replace non-protective antibodies in immune cells with antibodies protective against viruses?**
- **What was the key finding / take-home message?**
 - ❖ **Yes, we can efficiently engineer immune cells to produce protective antibodies that can control a virus.**
- **How is this important for an HIV cure?**
 - ❖ **Engineered immune cells could represent a single treatment that would provide a life-long source of protective antibodies.**

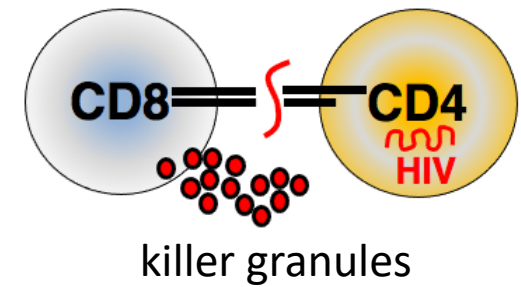
SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Do persistent infections (e.g. CMV) contribute to HIV persistence in people living with HIV?
- **What was the key finding / take-home message?**
 - ❖ We found that HIV-infected cells are triggered to expand during ongoing immune responses to other persistent infections.
- **How is this important for an HIV cure?**
 - ❖ Targeting the root cause of these ongoing immune responses could aid in the reduction of the latent reservoir size.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ We are trying to understand what it will take for the immune system to control HIV and prevent it from causing disease after antiretroviral therapy (ART) is stopped.
- **What was the key finding / take-home message?**
 - ❖ The immune cells that specialize in killing virus-infected cells (i.e. CD8+ T cells) do not respond in time to prevent and/or delay the recurrence of virus replication once ART is stopped. They are partially effective after the virus starts to replicate at high levels but at this stage, it is often too late to control the infection.
- **How is this important for an HIV cure?**
 - ❖ We are using this knowledge to design therapeutic interventions that will increase the ability of these virus-killing CD8+ T cells to intercept and control cells with latent-HIV infection early after ART is stopped with the idea that this will facilitate long-term control of virus replication.

SUMMARY FOR COMMUNITY



- **What key question was asked?**
 - ❖ What cellular pathways control the ability of CD8+ T cells to rapidly proliferate and raise an army of killer daughter cells when they see HIV-infected target cells?
- **What was the key finding / take-home message?**
 - ❖ We found that a protein that controls gene expression (called TCF-1) promotes CD8+ T cell proliferation, but this occurs at the expense of their killing function.
- **How is this important for an HIV cure?**
 - ❖ It may be important to understand how different HIV cure strategies balance T cell proliferation capacity and killing function.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **What is the best way(s) to measure SIV latent reservoirs in blood and tissues in order to target these reservoirs for a cure?**
- **What was the key finding / take-home message?**
 - ❖ **Tissue reservoirs persist in lymph nodes, tissues and brain in SIV infected, suppressed macaques.**
- **How is this important for an HIV cure?**
 - ❖ **The HIV latent reservoirs remain the major barrier to HIV Cure**

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Can viral replication be durably controlled after ART interruption by trapping CD8+ T cells in lymph nodes or administration of bnAbs in SIV/SHIV infected rhesus macaques?
- **What were the key findings / take-home messages?**
 - ❖ CD8+ T cells can be trapped in SIV infected lymph nodes, but do not effectively control viral replication after ART interruption
 - ❖ A single bnAb can temporarily delay virus rebound in SHIV/macaque model, much like in human clinical trials.
- ❖ **How is this important for an HIV cure?**
 - ❖ CD8+ T cell based HIV cure strategies will require immunomodulatory components to enable elimination of virus in lymphoid tissues.
 - ❖ A SHIV-macaque model that represents bnAb monotherapy allows new opportunities to dissect if and how bnAbs can suppress rebound

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **How do we measure the HIV-1 reservoir?**
- **What was the key finding / take-home message?**
 - ❖ **Different methods of measuring the reservoir show large differences**
 - ❖ **Combination of methods provides most accurate measurement**
- **How is this important for an HIV cure?**
 - ❖ **Goal of HIV-1 cure research is to reduce or silence the reservoir**
 - ❖ **Accurate measurement can guide such HIV-1 cure strategies**

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ What HIV transcript variants are produced by CD4+ cells harboring proviruses?
- **What was the key finding / take-home message?**
 - ❖ TranSeq successfully detects cell-associated 5' to 3' completed, genome-intact and unspliced (CGIU) transcripts. Even during uncontrolled viremia, CGIU transcripts only made up 2/37 (5%) of the viral transcriptome. No CGIU transcripts were detected in virologically suppressed study participants.
- **How is this important for an HIV cure?**
 - ❖ CGIU viral transcripts are rare. TranSeq provides a technology platform to obtain viral transcription profiles after latency reversal. Presence of CGIU viral transcripts may predict virologic rebound.

Summary for Community

What key question was asked?

- ❖ Can a novel HIV-1 based lentiviral vector (LV) encoding a multispecific anti-HIV CAR enable modified-T cells to recognize and broadly kill active HIV-infected cells while simultaneously protecting CAR-modified CD4⁺ T cells from HIV infection?

What was the key finding / take-home message?

- ❖ Multispecific duoCAR T cells **potently suppress** broad strains of HIV (up to 99%) in vitro, **persist and safely eliminate** HIV-infected cells in humanized mice (>97%), and are **protected** from HIV infection.

How is this important for an HIV cure?

- ❖ Anti-HIV duoCAR-T cell therapy is a powerful “living-drug” administered as a single infusion which is aimed at controlling HIV infection in the absence of ART in PLWH (functional cure).

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **Would trapping CD8⁺ T cells in lymph nodes of SIV-infected Rhesus Macaques help control viremia during antiretroviral therapy (ART) interruption?**
- **What was the key finding / take-home message?**
 - ❖ **Our data show that increased numbers of CD8⁺T cells in lymph nodes during ART interruption does not enable viral control.**
- **How is this important for an HIV cure?**
 - ❖ **Highlights the importance of combinatorial immune therapies to target the viral reservoir.**

Summary for Community

- What key question was asked?
 - When does the majority of the long-lived, latent HIV-1 reservoir form?
- What was the key finding / take-home message?
 - Most of the latent reservoir forms near the time ART is started, regardless of whether the virus is intact or defective.
- How is this important for an HIV cure?
 - Understanding how and when the latent reservoir forms helps us to think of strategies to prevent its formation

Summary for the community

- **Key question** : What was the role of T cell exhaustion in our **combinatorial intervention HIV cure study** that increased immune responses but failed to decrease virus rebound after stopping ART?
- **Key finding(s)**:
 - Monkeys given α PD-1 had better T cell responses to DNA vaccination in the blood, but these responses were short lived.
 - α PD-1 reduced PD1 signal in both blood and gut lymph nodes (MLN) but did not reduce other exhaustion markers (TIGIT, TIM3, CTLA4, LAG3).
 - Higher TIGIT on T cells before DNA vaccination led to worse T cell vaccine responses.
- **Take home message**: Reversing T cell exhaustion with both α PD-1 and α TIGIT may increase immune responses to DNA vaccination, taking us one step closer to a functional cure.

α PD-1

Exhaustion-reversal: revives 'tired' T cells



DNA Vaccination

Targets T cells to features important to viral growth



GS-986

infected cells are 'seen' and destroyed



CCR5-editing

protects CD4 cells from infection



SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Is the HIV that is hiding in places such as the male genital tract different from the HIV in the rest of the body?
- **What was the key finding / take-home message?**
 - ❖ We need more samples to determine definitively.
- **How is this important for an HIV cure?**
 - ❖ HIV in the male genital tract may contribute to persistent inflammation and co-morbidities in PWH and may be more difficult to eradicate.

SUMMARY FOR COMMUNITY

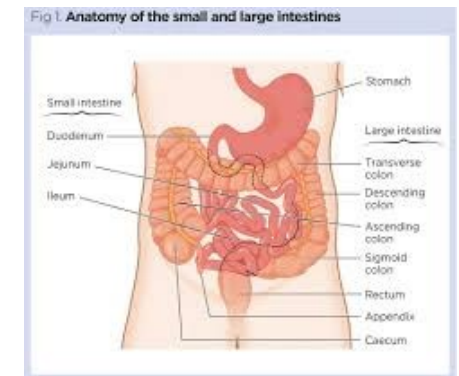
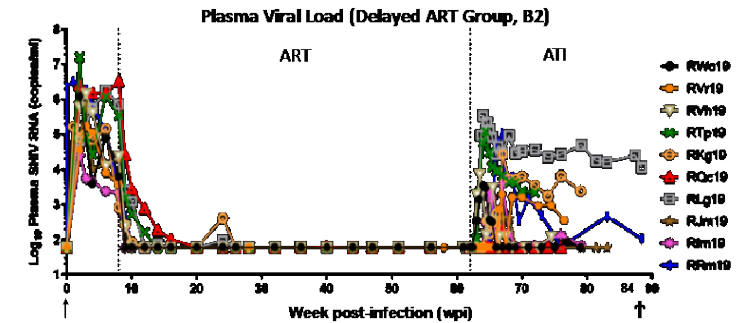
- Are measurements taken before the start of an analytical treatment interruption (ATI) study impacting when HIV-1 rebound will occur?
- Participants who had lower viral loads in acute infection, before they started treatment, rebounded later than those with higher viral loads
- If we find measurements that can predict when someone may rebound, we can reduce the need for ATI studies

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Which type of CD4 T cell makes the largest contribution to total viral levels in infants living with HIV-1?
- **What was the key finding / take-home message?**
 - ❖ In an animal model of pediatric HIV-1, about half of all virus was found in naïve CD4 T cells
- **How is this important for an HIV cure?**
 - ❖ HIV-1 may hide in a cell type that is abundant in infants, yet has been less-studied in cure research

SUMMARY FOR COMMUNITY

- **What is the origin and predictors of virus rebound after antiretroviral treatment interruption in children living with HIV?**
Use nonhuman primate model of infant HIV infection to:
 - ❖ Determine location in the body that the virus first reactivates
 - ❖ Define a blood test that would predict when virus will reactivate after stopping therapy
 - ❖ Determine immune responses that could be enhanced through vaccination to block virus reactivation
- **What was the key finding / take-home message?**
 - ❖ The GI tract is a major contributor to viral reactivation in children
 - ❖ The ability to neutralize the virus used to infect the infants was associated with increased time to viral reactivation
- **How is this important for an HIV cure for children?**
 - ❖ GI tract should be targeted by HIV cure therapies for children
 - ❖ Vaccines used to enhancing immunity that can prevent viral rebound should focus on antibodies that can neutralize the infecting virus



SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ The goal of this study was to investigate the kinetics of HIV-specific antibodies in infant rhesus macaques on antiretroviral drugs
- **What was the key finding / take-home message?**
 - ❖ We observed that 50% of infant macaques developed autologous neutralization (neutralize their own virus) while they were on treatment. The levels of autologous antibodies were associated with delay time to rebound after treatment interruption
- **How is this important for an HIV cure?**
 - ❖ Boosting neutralizing antibody responses through immunization should be explored as a potential strategy towards a functional cure in children

SUMMARY FOR COMMUNITY

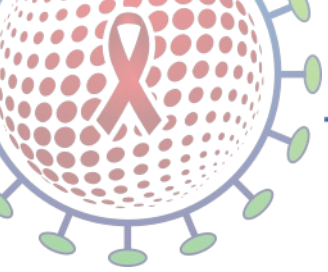
- **What key question was asked?**
 - ❖ Our objectives were (i) to characterize the clinical evolution of people durably controlling HIV-1 despite interrupting antiretroviral therapy, and (ii) to identify potential virologic, immunologic or genetic factors responsible for such control
- **What was the key finding / take-home message?**
 - ❖ Early cART initiation and some genetic factors (associated with the innate immune response) favor post-treatment control of infection.
 - ❖ Post-treatment control occurs despite the presence of replication competent virus.
 - ❖ There are two paths towards post-treatment control:
 - ❖ One is “silent”, characterized by continuously undetectable viral loads, stable CD4+ T cell counts and weak immune activation and inflammation. In some cases this is associated with a progressive decline in the frequency of infected cells.
 - ❖ The other is “active”, characterized by transient periods of low level viremia and the development of HIV-specific T cells responses and antibodies with neutralizing activity.
- **How is this important for an HIV cure?**
 - ❖ Post-treatment controllers in our study have been living without cART for over 12 years (some are close to 20 years off cART!!) These persons offer the first opportunity to understand the challenges of living for long periods of time with undetectable viral load upon treatment interruption;
 - ❖ Some of the factors associated with post-treatment control in our study may lead to new therapeutic interventions aiming HIV remission.

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ How does the size of the reservoir change over time in children living with HIV?
 - ❖ Does very early treatment of infants within two days of life affect the size of the reservoir
- **What was the key finding / take-home message?**
 - ❖ We found different patterns in the changes in the size of the reservoir in children
 - ❖ some children show the reservoir getting smaller over time
 - ❖ others show the reservoir expanding over time
 - ❖ Treating infants within the first two days of life makes the reservoir smaller within the first two years of age
- **How is this important for an HIV cure?**
 - ❖ Treatments for HIV cure may work better in children when reservoirs are small

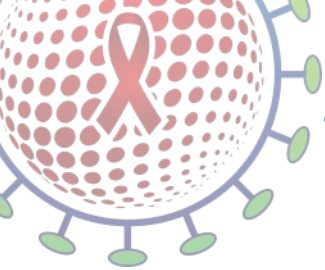
SUMMARY FOR COMMUNITY

- **What key questions were asked?**
 - ❖ Which type of cells that are infected initially by incoming SIV virions serve as a persistent reservoir that can fuel rebound viremia after early ART (started on day 3) is stopped many months later?
 - ❖ Can rebound viremia be blunted when suppressive ART stops by inhibiting mTOR activity, a master regulator of cell growth, with now-available drugs or compounds already in clinical trials?
 - ❖ Can we learn how cells regulate levels of a defensive protein (APOBEC3s) that can make viruses reactivated from reservoir cells non-infectious when they are present in those cells?
- **What were the key findings / take-home messages?**
 - ❖ Infected myeloid cells, rather than infected T cells, seem to predominate in the early reservoir of persistent SIV-infected cells.
 - ❖ Inhibiting mTOR blocked target T cell susceptibility to HIV in cell culture, but also increased production of mediators of both inflammation and blood clotting from cultured blood monocytes. This unexpected monocyte-produced blood clotting risk was prevented in cell culture by adding what could be an easy-to-take dietary supplement to the mTOR inhibitor.
 - ❖ Uninfected cell APOBEC3 levels are regulated by degrading those proteins using a mechanism that parallels how retroviruses degrade APOBEC3s, and has some important differences from the retroviral mechanism.
- **How is this important for an HIV cure?**
 - ❖ We aim to develop new strategies for research aiming to end virus persistence in order to stop the inflammation triggered by persisting virus that causes conditions in PLWH categorized as “accelerated aging” (heart and vascular diseases, cancer, etc) - without worsening such inflammation during efforts at minimizing viremia rebound after stopping ART.



Summary

- We asked if T cells can make a contribution to controlling HIV after treatment is stopped.
- We found that certain robust and atypical T-cell response likely do contribute to post-treatment control.
- This is important to HIV cure because many cure strategies are thought to require a component of ongoing “immunosurveillance.”



Summary

- T cells can act in different ways to fight HIV, employing various “effector functions”
- Using a novel technique, we identified more, and functionally more diverse T cells.
- Their presence correlated with viral load and reservoir size in the blood of PLWH
- It remains to be shown whether these cells can be induced by therapeutic vaccination and how they contribute to “immunosurveillance” of HIV

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ **Can people with HIV (PWH) at the end of their life help with HIV cure research?**
- **What was the key finding / take-home message?**
 - ❖ **PWH are often interested in participating in HIV cure research at the end of their lives and their contribution is highly valuable**
- **How is this important for an HIV cure?**
 - ❖ **PWH who participate in cure research with body donation is very helpful to figure out where and how HIV hides throughout the body**

SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Experimental chemicals that “wake up” dormant HIV are often called latency reversing agents. Natural killer cells are an important part of the immune system that can target and destroy cells actively expressing HIV. We asked whether combinations of these two approaches could slow down or stop HIV re-emergence if therapy is stopped.
- **What was the key finding / take-home message?**
 - ❖ We found that chemicals that wake up dormant HIV during therapy can delay virus re-emergence (rebound) after therapy is stopped, and this delay in rebound is improved if anti-HIV immune cells are also added.
- **How is this important for an HIV cure?**
 - ❖ These animal model results indicate that proposed “kick and kill” or “activation/elimination” strategies show promise as components of HIV cure approaches.

BioMark SUMMARY FOR COMMUNITY

- **What key question was asked?**
 - ❖ Can we identify biological signatures in the blood stream that predict how a person and their virus will respond when antiretroviral drugs are stopped? Will the virus rebound quickly, slowly, or ideally not at all?
- **What was the key finding / take-home message?**
 - ❖ We discovered that the presence of special immune cells in the blood stream (specific subsets of T cells and NK cells) and the presence of high levels of free circulating DNA in the plasma predict a longer time-to-rebound of the virus after stopping ART.
- **How is this important for an HIV cure?**
 - ❖ Biological signatures in blood predicting a delayed time to HIV rebound can help guide the development of new cure strategies and provide key insights into those processes that can successfully control the virus in the absence of ART.