

# PEMBROLIZUMAB INDUCES HIV LATENCY REVERSAL IN HIV+ INDIVIDUALS ON ART WITH CANCER

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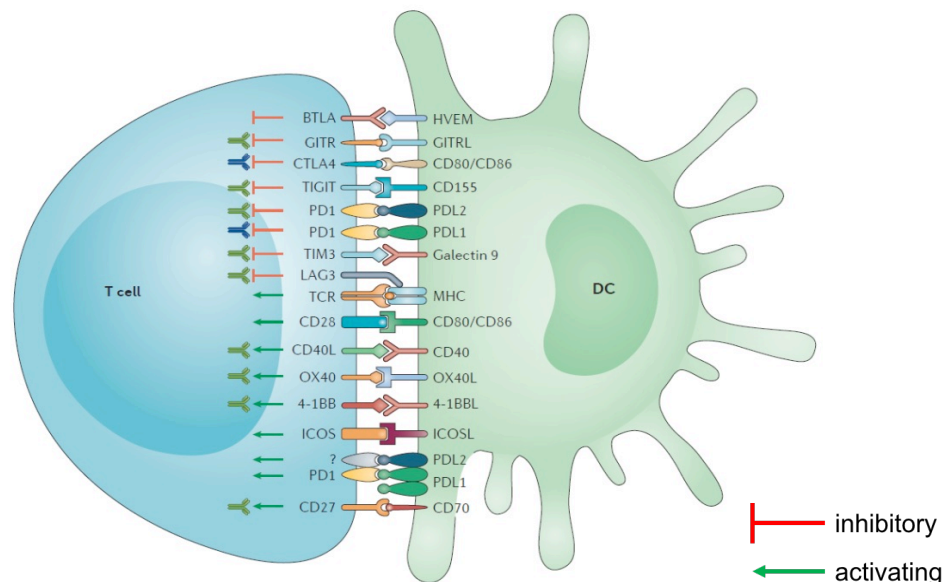


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# Background: PD-1

- PD-1 is an inhibitory checkpoint molecule on T-cells that inhibits immune responses against cancers and viral infections
- Monoclonal antibodies targeting PD-1 or PD-L1 are approved for a growing number of cancer indications

## Checkpoint Proteins Regulate T-cell Function

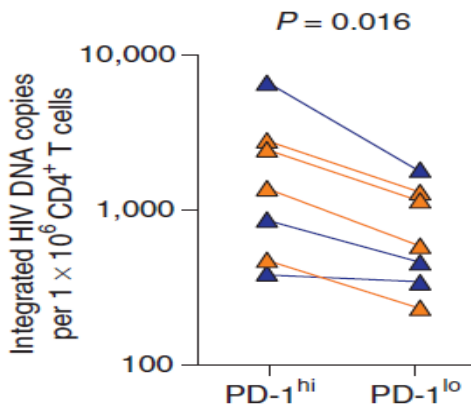


Wykes M and Lewin SR, *Nat Rev Immunol* 2017

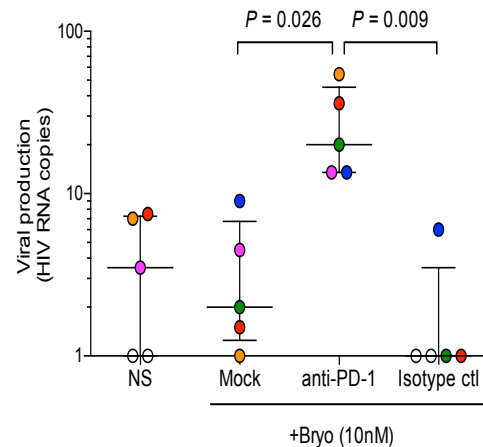
# HIV infected CD4<sup>+</sup> T-cells Enriched for PD-1

- PD-1 upregulated in HIV
- HIV DNA and unspliced RNA are enriched in PD-1<sup>+</sup> cells in blood and lymph nodes in HIV+ individuals on ART
- **We hypothesized anti-PD-1 would lead to latency reversal *in vivo***

## HIV DNA Enriched in PD-1<sup>hi</sup> CD4<sup>+</sup>



## Anti PD-1 Can Reverse HIV Latency *ex vivo*

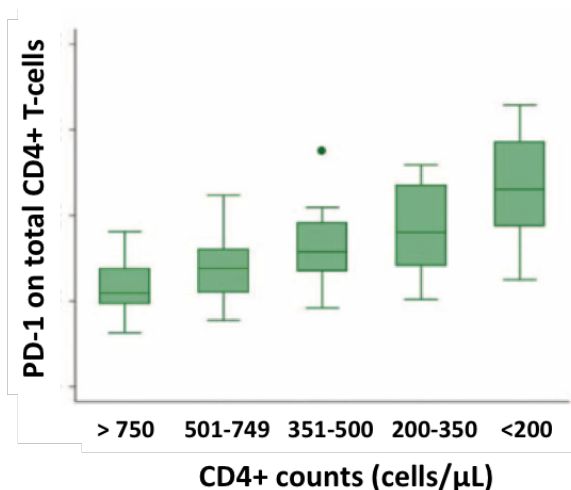


Chomont, *Nature Med* 2009; Fromentin et al., *Nature Comms* 2019;  
Banga, *Nature Med* 2016; McGarry, *Immunity* 2017; Chomont, *Plos Pathog*, 2019

# Cancer Immunotherapy Trials Network-12 (CITN-12)

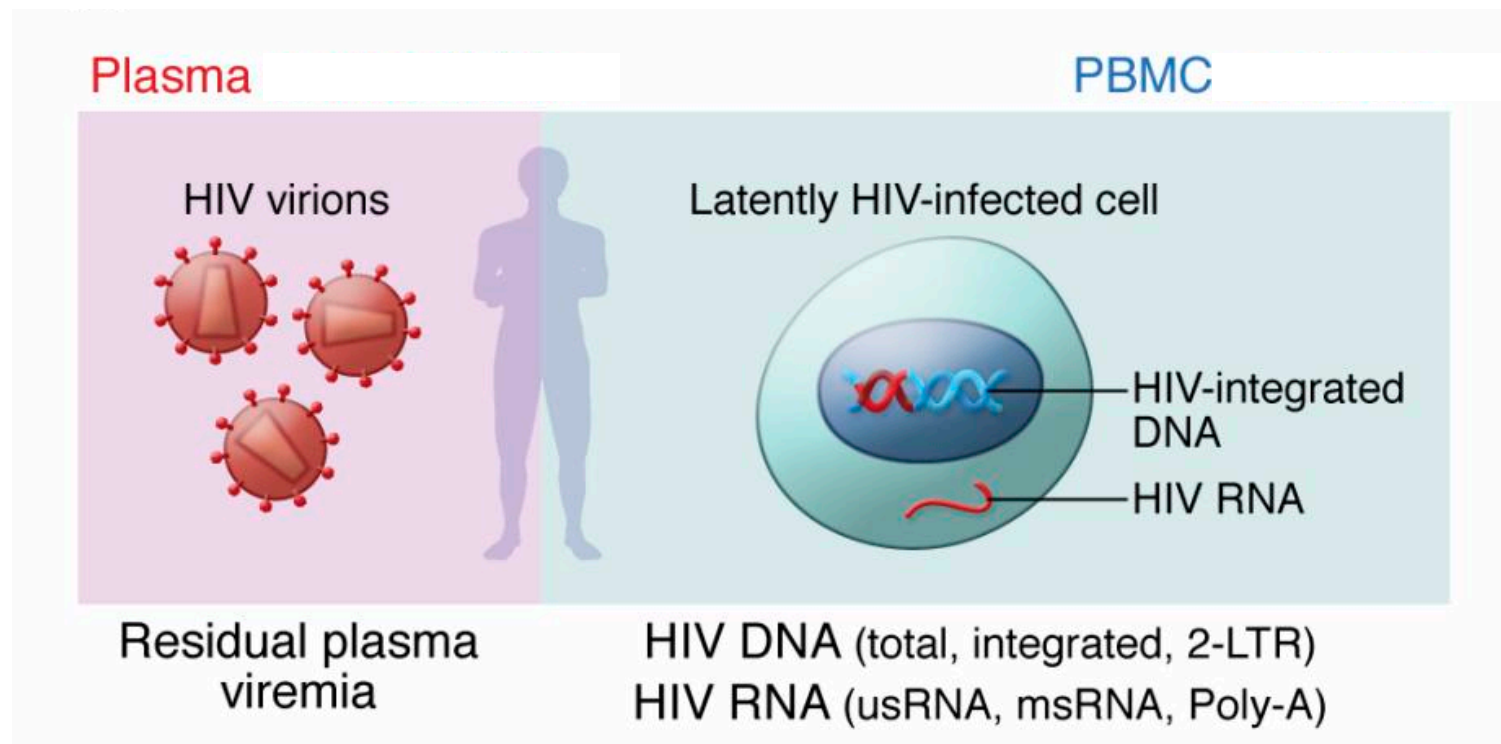
- CITN-12 is a multicenter phase I study evaluating the monoclonal antibody, pembrolizumab, in participants with HIV and advanced cancers
- Participants on ART for  $\geq 4$  weeks with suppressed HIV
- Safety evaluated across a range of CD4 counts
  - Cohort 1: 100-199 CD4<sup>+</sup> T cells/ $\mu$ L
  - Cohort 2: 200-350 CD4<sup>+</sup> T cells/ $\mu$ L
  - Cohort 3:  $>350$  CD4<sup>+</sup> T cells/ $\mu$ L

PD-1 Inversely Related to CD4<sup>+</sup> in HIV



Cockerham. *AIDS*, 2014

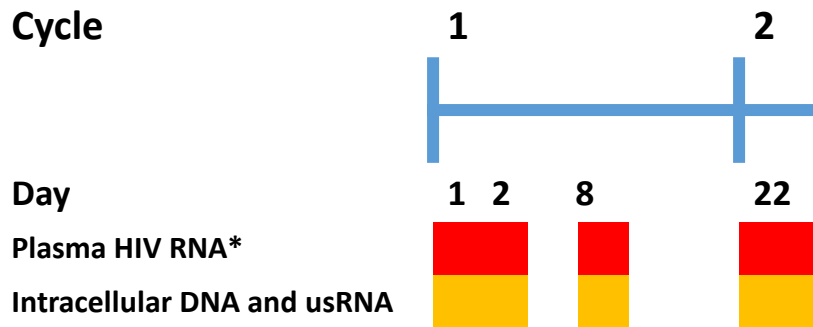
# Measuring HIV Latency Reversal *in vivo*



# Leveraging CITN-12 to Evaluate HIV Latency Reversal

- Cell associated HIV DNA measured in peripheral CD4+ T-cells
- Cell associated unspliced HIV *gag* RNA measured in peripheral CD4+ T-cells
- Plasma HIV RNA measured in blood using PCR for HIV *gag*

## Blood Sampling Schema



\* on day of administration: before and 2 hours after pembrolizumab

Lewin S, *JAIDS* 2008, Cillo, *PNAS* 2014



# Statistical Analysis

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- Kinetics of HIV plasma RNA, intracellular usRNA, usDNA, and usRNA/vDNA were evaluated by negative binomial regression
- Pairwise correlation between assays were compared by Pearson's correlation coefficient

# Participant Characteristics

|                                      | All            | Cohort 1<br>CD4 <sup>+</sup> 100-199 / $\mu$ L | Cohort 2<br>CD4 <sup>+</sup> 200-350 / $\mu$ L | Cohort 3<br>CD4 <sup>+</sup> >350 / $\mu$ L |
|--------------------------------------|----------------|------------------------------------------------|------------------------------------------------|---------------------------------------------|
| Number                               | 32             | 8                                              | 12                                             | 12                                          |
| Age (median, IQR*)                   | 57 (49, 62)    | 53.5 (46, 61)                                  | 54.5 (49, 61)                                  | 58 (52, 64)                                 |
| Male                                 | 29             | 7                                              | 11                                             | 11                                          |
| Race                                 |                |                                                |                                                |                                             |
| White                                | 19             | 5                                              | 9                                              | 5                                           |
| Black / African American             | 10             | 2                                              | 3                                              | 5                                           |
| Other / Unknown                      | 3              | 1                                              | 0                                              | 2                                           |
| HIV viral load (copies/ml)           |                |                                                |                                                |                                             |
| Undetected or <20 copies/ml          | 28             | 8                                              | 10                                             | 10                                          |
| $\geq$ 20 copies/ml                  | 4              | 0                                              | 2                                              | 2                                           |
| Baseline CD4 Count (median, IQR)     | 272 (204, 477) | 152 (119, 164)                                 | 239 (216, 289)                                 | 516 (425, 649)                              |
| Baseline CD4/CD8 Ratio (median, IQR) | 0.5 (0.4, 0.9) | 0.5 (0.4, 0.5)                                 | 0.4 (0.3, 0.7)                                 | 0.9 (0.5, 1.5)                              |

\*IQR; Intra-quartile range (25<sup>th</sup> and 75<sup>th</sup> percentiles)



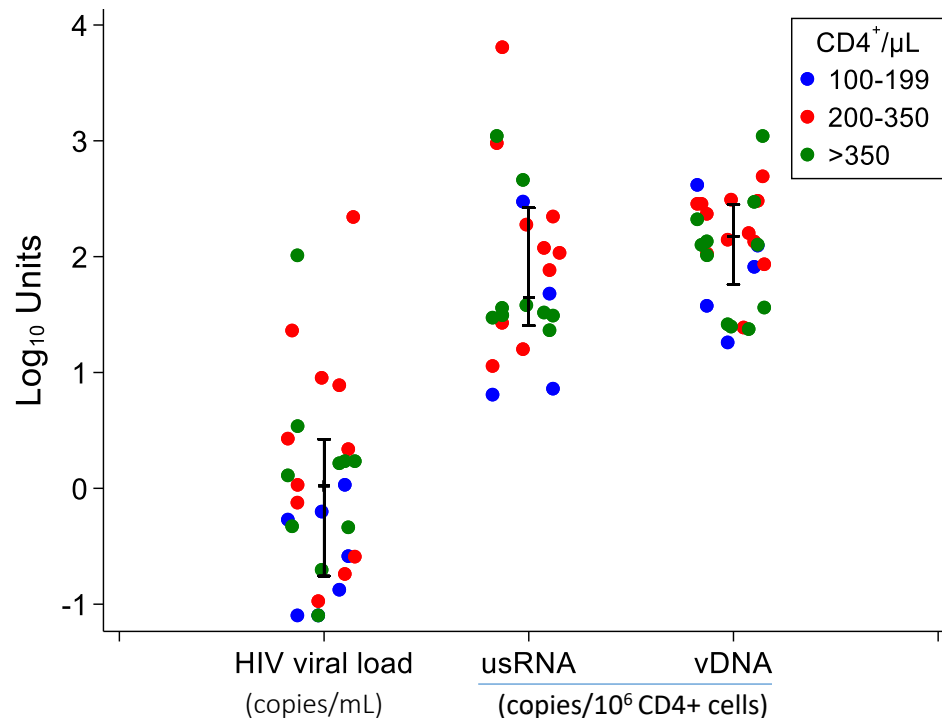
# Tumors

|                                 | Cohort 1<br>CD4+ 100-199 / $\mu$ L | Cohort 2<br>CD4+ 200-350 / $\mu$ L | Cohort 3<br>CD4+ >350 / $\mu$ L | Total |
|---------------------------------|------------------------------------|------------------------------------|---------------------------------|-------|
| <b><u>Total</u></b>             | 8                                  | 12                                 | 12                              | 32    |
| <b><u>AIDS-Defining</u></b>     |                                    |                                    |                                 | 11    |
| Kaposi sarcoma                  | 0                                  | 2                                  | 4                               | 6     |
| DLBCL                           | 0                                  | 1                                  | 2                               | 3     |
| Primary effusion lymphoma       | 1                                  | 1                                  | 0                               | 2     |
| <b><u>Non-AIDS Defining</u></b> |                                    |                                    |                                 | 21    |
| Anal cancer                     | 4                                  | 2                                  | 0                               | 6     |
| Squamous Cell Carcinoma Skin    | 1                                  | 1                                  | 1                               | 3     |
| Lung                            | 0                                  | 1                                  | 1                               | 2     |
| Hepatocellular carcinoma        | 0                                  | 1                                  | 0                               | 1     |
| Tonsil                          | 0                                  | 1                                  | 0                               | 1     |
| Cholangiocarcinoma              | 0                                  | 1                                  | 0                               | 1     |
| Breast                          | 1                                  | 0                                  | 0                               | 1     |
| Osteosarcoma                    | 1                                  | 0                                  | 0                               | 1     |
| Pancreatic                      | 0                                  | 0                                  | 1                               | 1     |
| Adenocystic carcinoma           | 0                                  | 0                                  | 1                               | 1     |
| Bladder cancer                  | 0                                  | 0                                  | 1                               | 1     |
| Prostate                        | 0                                  | 1                                  | 0                               | 1     |
| Urothelial carcinoma            | 0                                  | 0                                  | 1                               | 1     |

# Baseline HIV Measures

|                                                      | Median | IQR           |
|------------------------------------------------------|--------|---------------|
| HIV plasma RNA<br>(copies/ml)                        | 1      | (0.17 – 2.65) |
| HIV usRNA<br>(copies/ $10^6$ CD4 <sup>+</sup> cells) | 43     | (15-133)      |
| HIV vDNA<br>(copies/ $10^6$ CD4 <sup>+</sup> cells)  | 76     | (55 - 149)    |

- No correlation between assays  
(all  $P > 0.05$ )



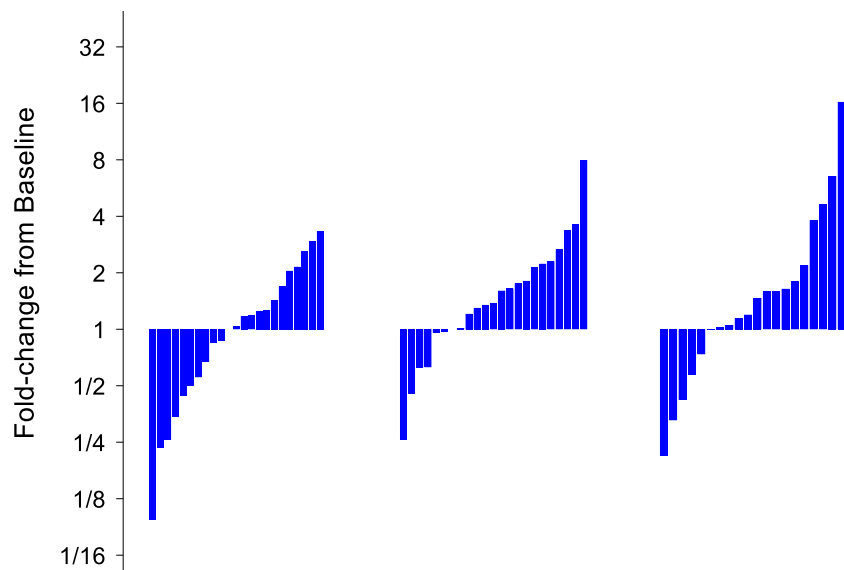
# Waterfall Plots of Fold Change HIV RNA

## Unspliced Intracellular HIV RNA

Day 2

Day 8

Day 22

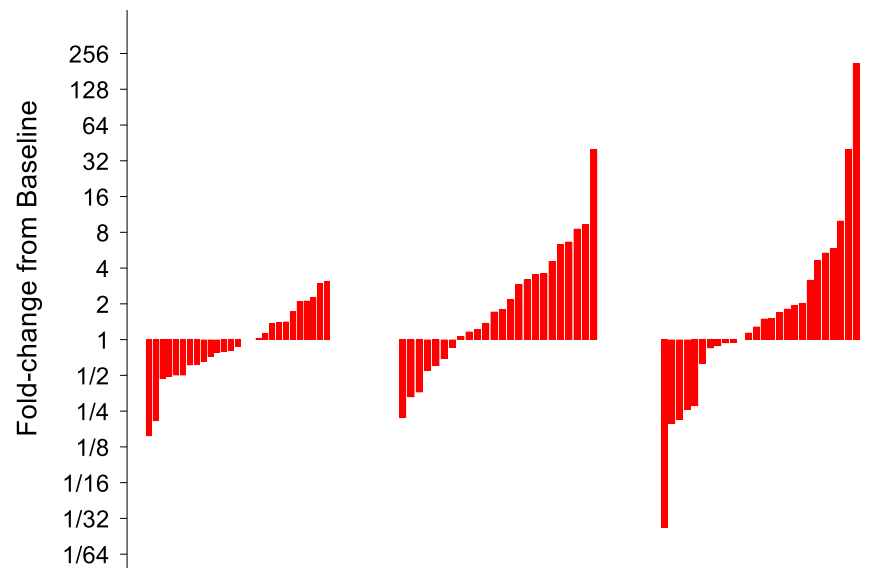


## Plasma HIV RNA

Day 2

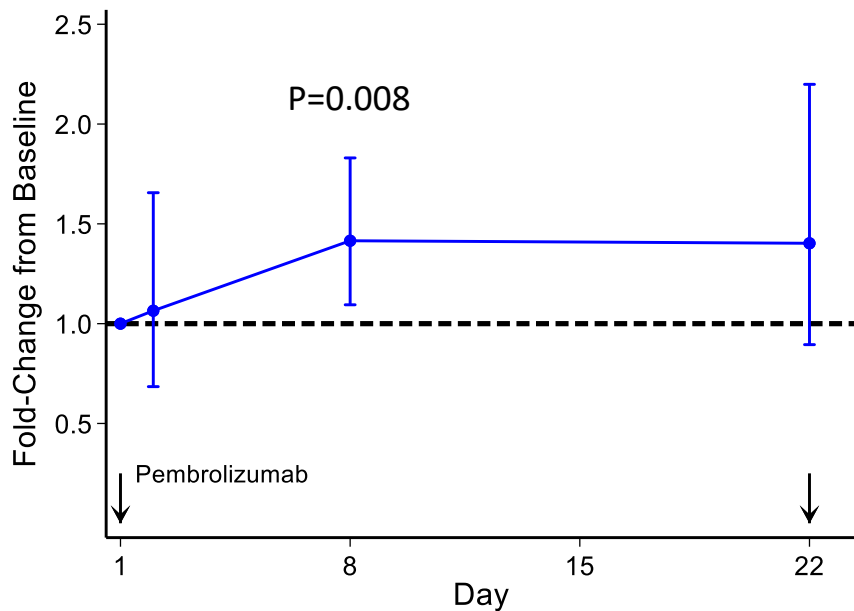
Day 8

Day 22

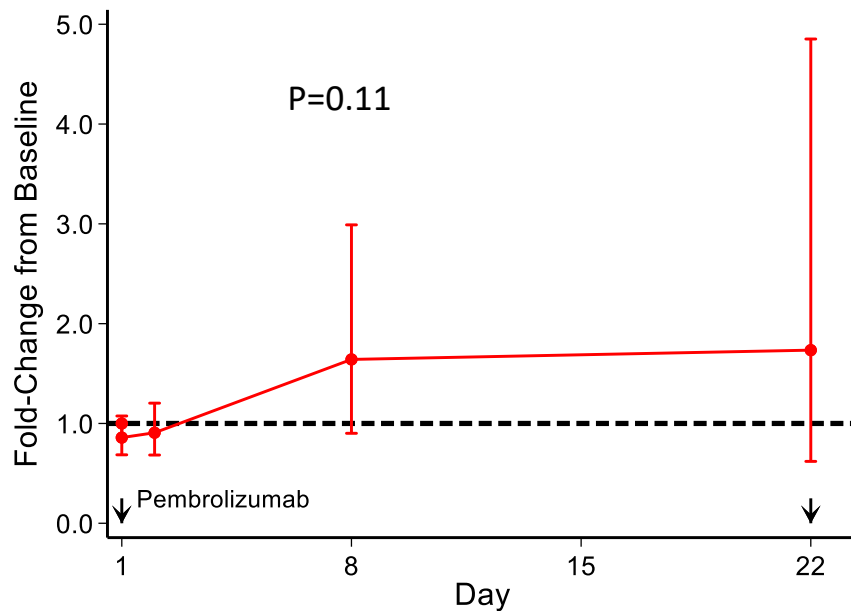


# HIV RNA After Pembrolizumab

## Unspliced Intracellular HIV RNA

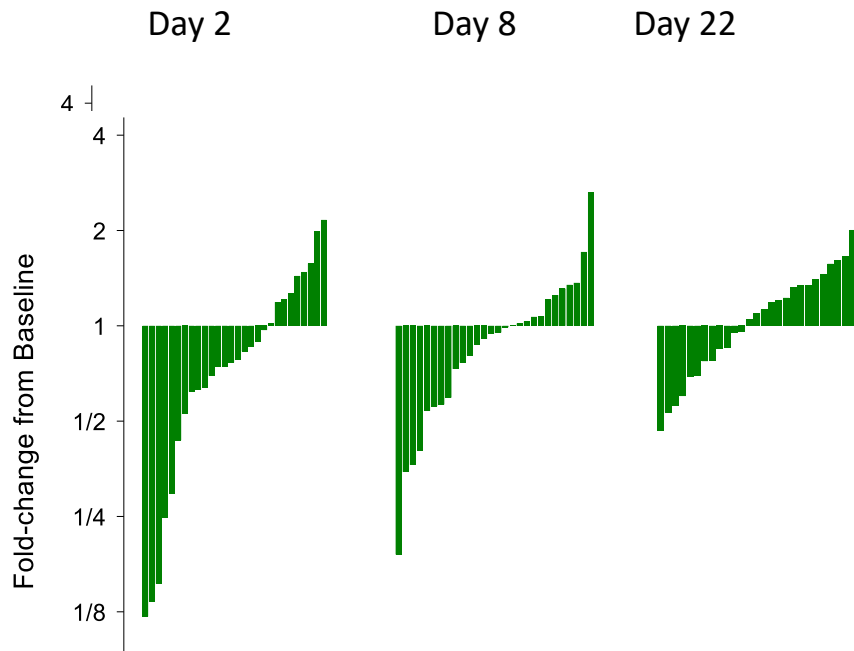


## Plasma HIV RNA

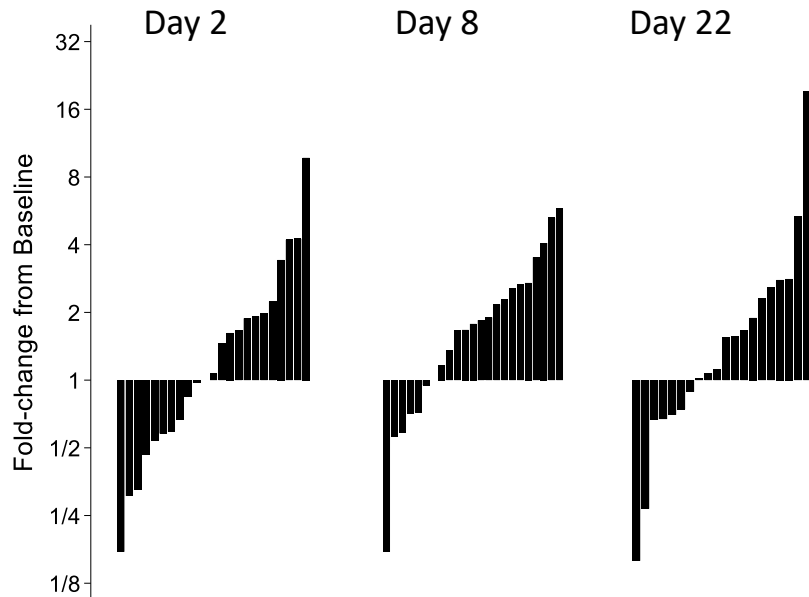


# Fold Change HIV DNA and usRNA/DNA

## Intracellular HIV DNA

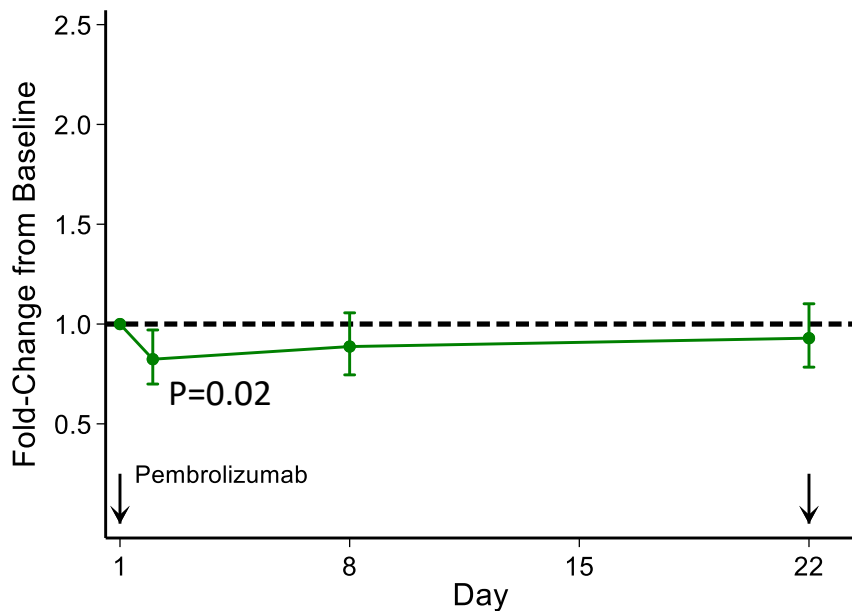


## Intracellular HIV usRNA/DNA

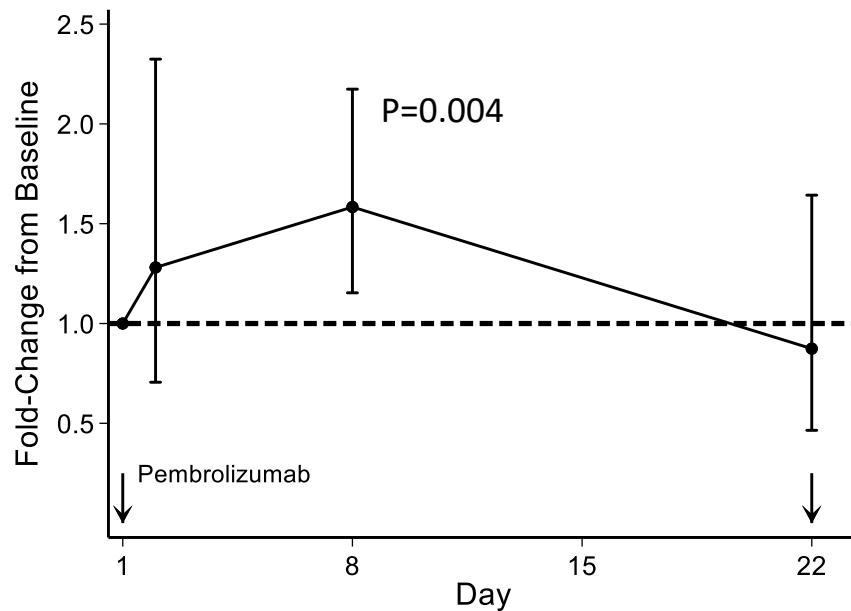


# HIV DNA and usRNA/DNA after Pembrolizumab

## Intracellular HIV DNA



## Intracellular unspliced RNA / DNA



# Conclusions

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- In CITN-12, pembrolizumab led to transient increase in HIV transcription in CD4<sup>+</sup> T-cells *in vivo* in individuals on ART, consistent with latency reversal
- Early decrease in HIV DNA was observed after pembrolizumab
- Evaluation of the longer term effects pembrolizumab on HIV persistence and HIV specific immunity are ongoing
- Further evaluation of monoclonal antibodies against PD-1 or PD-L1 as a strategy for HIV cure is warranted



# Acknowledgements

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