HIV-Specific Neutralizing Antibody Responses after Acute and Early ART Initiation

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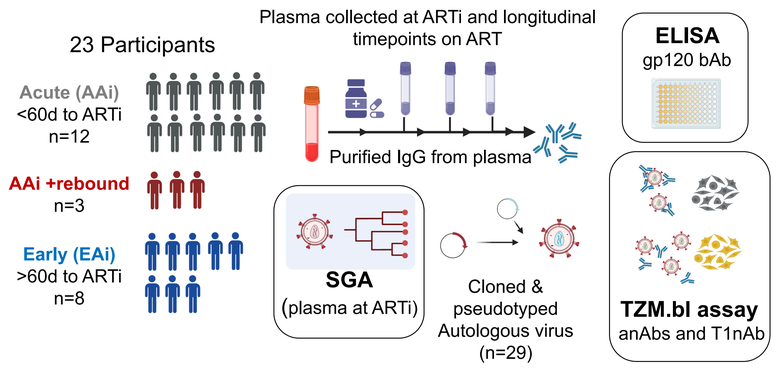
Background

- Early ARTi restricts reservoir size and diversity
- Non-neutralizing Ab with effector function develop after Acute ARTi[1]
- Autologous neutralizing antibodies (anAb) develop after Early ARTi[2]
- bnAbs inhibit replication of sensitive virus *in vivo*[3]
- anAbs prevent outgrowth of sensitive virus in *ex vivo* stimulated T cells[4]
- anAb responses with sufficient breadth and potency may have therapeutic potential in the setting of Early ARTi

Here we investigated how differential timing of ARTi in Acute and Early HIV disease affects development of binding Ab, Tier 1 nAb, and autologous nAb responses on ART, rooting analysis in viral populations present at ARTi

Methods



23 participants from UCSF Treat Acute HIV Cohort (Sulggi Lee) comprised study cohort. Participants initiated ART 13-128 days after infection[5]. Participants were stratified into 'Acute ARTi (AAi, <60 days to ARTi) or Early ARTi (EAi, >60 days to ARTi). Plasma was collected at day of ARTi and longitudinally through ART suppression. Single genome sequencing (SGS) of plasma virus at ARTi was performed to identify TF or early viruses, which were cloned and pseudotyped. Plasma IgG from longitudinal timepoints was tested for autologous or tier 1 virus (MN, SF162) neutralization by TZM.bl assay and binding antibodies by ELISA.

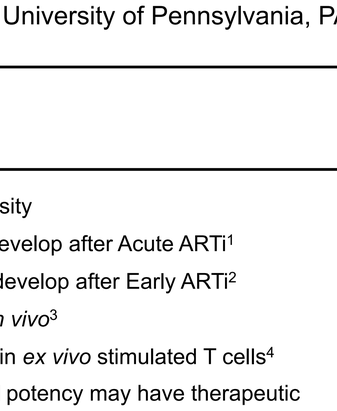
Results

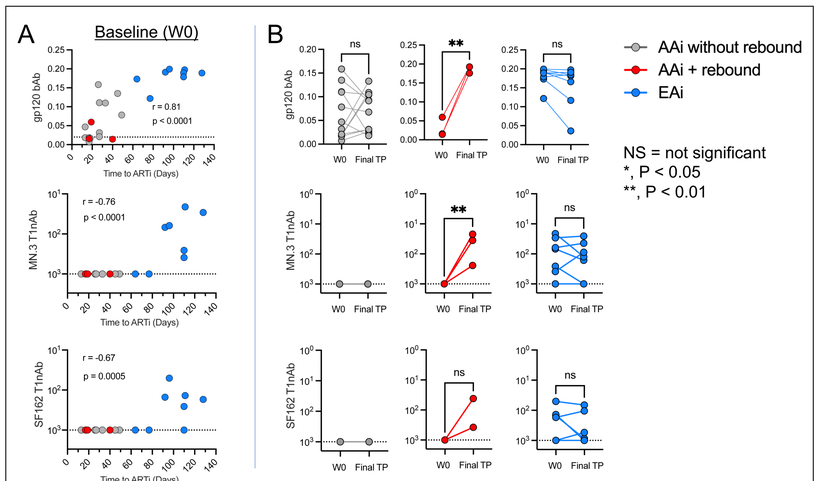
Viral Load Kinetics

Viral load at ARTi was significantly higher in the AAi group (4,142 to >10,000,000 copies/mL, median = 1,213,637 copies/mL), compared to the EAi group (9,525 to 297,362 copies/mL, median = 68,324 copies/mL) (p = 0.02, two-tailed Mann-Whitney).

First undetectable viral load (<40 copies/mL) trended later in AAi (median = 8 weeks) compared to EAi (median = 4 weeks) (p = 0.08, two-tailed Mann-Whitney).

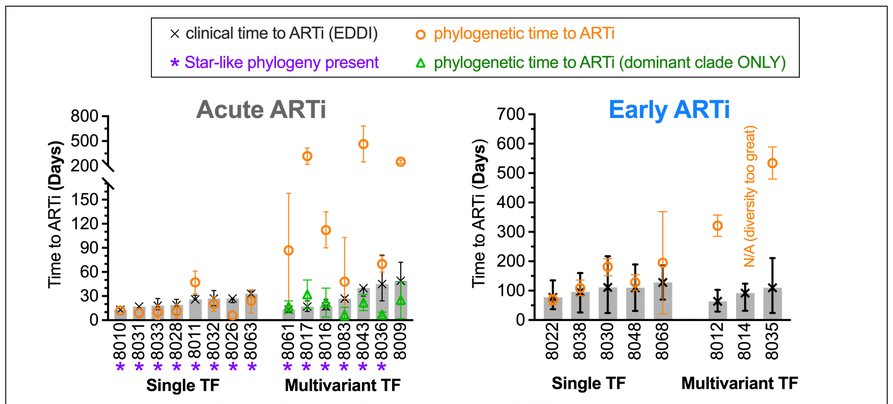
Three AAi participants (8016, 8028, and 8043) experienced unplanned rebound viremia >1,000 copies/mL After first negative viral load measurement on ART and were analyzed as a separate subgroup.





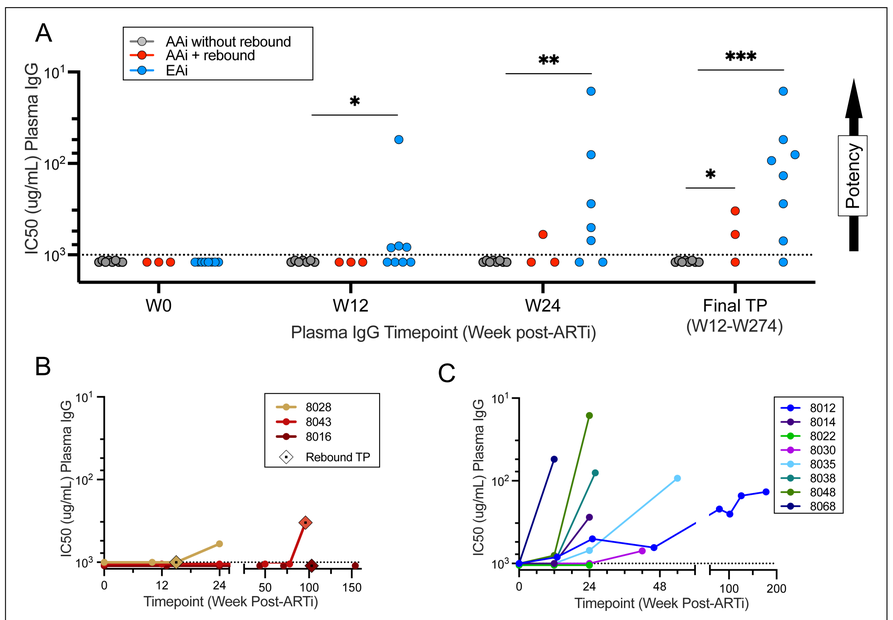
Binding (bAb) and Tier 1 Neutralizing Ab (T1nAb) Responses

(A) gp120 bAb and T1nAb at baseline (Week 0, day of ARTi). Gp120 bAb increase with longer time to ARTi, and T1nAb are only present in participants with >90 days to ARTi. Spearman correlation. (**B**) Change in bAb and T1nAb between Week 0 and Final TP (12-274 weeks post-ARTi) for individual participants. bAb increase in some AAi participants, while T1nAb only increase with rebound. Wilcoxon matched-pairs signed rank test.



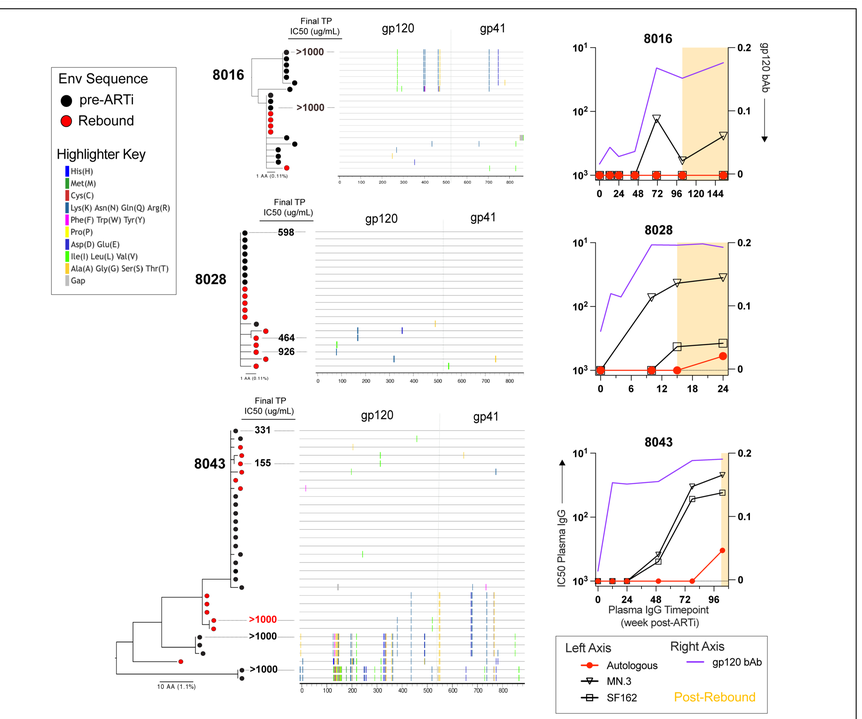
Sequencing of Viral populations at ARTi

Time to ARTi estimated by clinical testing (EDDI algorithm)[5] was highly aligned with time to ARTi estimated by viral population diversity using a model of random virus evolution (LANL Poisson-Fitter Tool)[6] Star-like phylogeny, indicating a lack of selective pressure, was present in 14/15 AAi participants and no EAi participants. Multivariant infection was identified in 10/23 participants (43%).



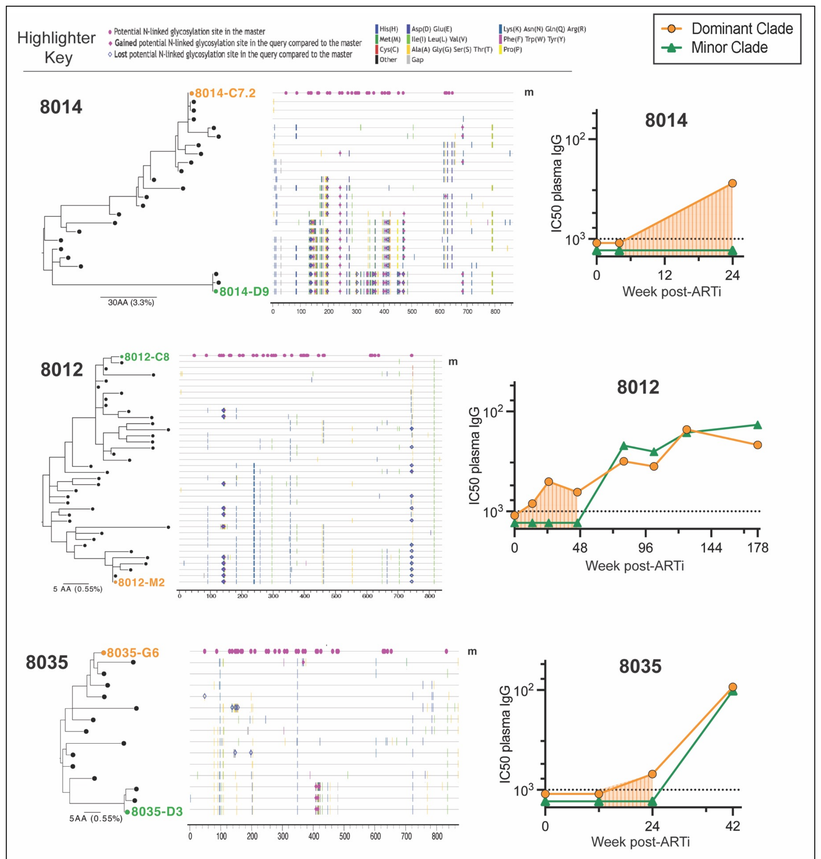
Autologous Neutralizing Antibody (anAb) Responses

(A) AnAb responses absent at time of ARTi in all participants, likely due to absent anAbs or existing anAbs selecting for escape variants. anAbs then develop on ART in 2/3 AAi with rebound participants and 7/8 EAi participants, but no AAi without rebound participants. Fisher Exact Test (**B,C)** anAb kinetics demonstrate that in AAi participants, anAbs only develop at or after rebound episode. In EAi participants, anAbs develop 12-40 weeks after ARTi, and potency increases over many weeks on continued suppressive ART.



In Acute ARTi, anAbs can be Elicited by Rebound Viremia

Amino Acid phylogenetic trees for AAi participants incorporating virus from ARTi (black nodes) and virus from rebound timepoint (red nodes). Participants 8028 and 8043 developed anAbs and show slightly increased diversity in rebound populations. Neutralization of rebound virus by final timepoint plasma IgG was assessed, showing a recombinant escape lineage in 8043 and perhaps early escape in 8028.
On right is shown binding Ab, T1nAb, and anAb responses over time in each participant.



anAbs Gain Autologous Breadth over Long Periods on ART

Three EAi participants who developed anAbs after ARTi were identified as having multivariant transmission. (**Left**) Amino acid phylogenetic trees and highlighter plots for these individuals, with dominant clade (>50% of viral population) labeled in orange, and minor clade(s) labeled in green. Many recombinant sequences are seen. (**Right**) Autologous neutralization by TZM.bl assay of dominant and minor clade by plasma IgG collected at ARTi and longitudinal timepoints shows that initial anAbs target dominant clade, but over long periods of time (as shown in 8012 and 8035), anAbs gain autologous breadth to also neutralize minor clade.

Conclusions

- Kinetics of binding, tier 1, and autologous nAb responses after Acute/Early ARTi are distinct.
- At baseline, Early ARTi possess *greater binding Ab, T1nAb, and sequence diversity* suggesting existing anAbs and immune escape compared to Acute ARTi.
- In **Acute ARTi** anAbs do not develop on ART, but can be elicited by rebound.
- In **Early ARTi** anAb responses mature over months to years on ART, increasing in *potency and autologous breadth.*

These findings suggest a potential role for therapeutic vaccination to boost and broaden anAbs to sufficiently restrict the narrow diversity of reservoir virus after Acute/Early ARTi.

References

1.) Mitchell et al. J Clin Invest, 2022. 132(1). 2.) Esmaeilzadeh et al. Sci Transl Med. 2023 May 10;15(695). 3.) Sneller et al. Nature 606, 375–381 (2022). 4.) Bertagnolli. Proc Natl Acad Sci U S A. 2020 Dec 15;117(50):32066-32077 5.) Grebe et al. BMC Infect Dis 19, 894 (2019)). 6.) Giorgi et al. BMC Bioinformatics 2010 Oct 25;11:532

Methods image prepared with Biorender software

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