AUTOLOGOUS NEUTRALIZING ANTIBODIES DEVELOP AFTER EARLY BUT NOT ACUTE ART INITIATION

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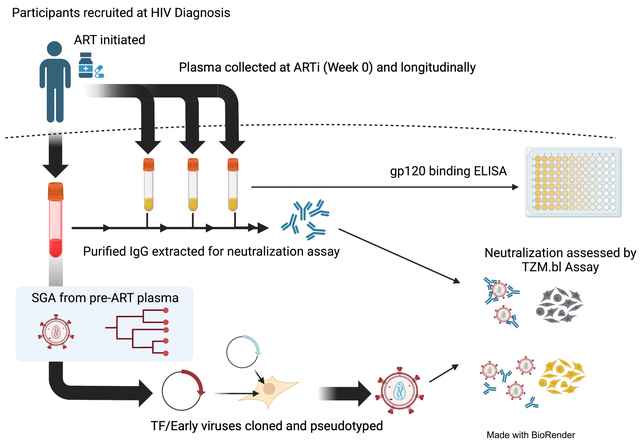
BACKGROUND

- Antiretroviral therapy initiation (ARTi) in acute/early HIV infection limits reservoir size and diversity, preserves host immunity, and reduces the risk of transmission.
- Early ARTi may limit development of HIV-specific immune responses, and the effects of early ARTi on autologous neutralizing antibody (anAb) development and persistence is unclear.
- Here, we identified TF or early plasma virus populations in individuals with acute/early ARTi and assessed the longitudinal antibody responses to these autologous TF/ early viruses

METHODS



Participants (n=15, all male) were selected from the UCSF Treat Acute HIV. ARTi 17-128 days after estimated date of diagnosable infection (EDDI, calculated by EDDI online tool (https://tools.incidence-estimation.org/idt/). Plasma was collected on day of ARTi and longitudinally for 3-36 months. Single genome amplification (SGA) of pre-ART plasma virus was used to identify TF or representative early env (gp160) sequences, which were cloned and pseudotyped. Purified plasma IgG from longitudinal timepoints was used to test for autologous neutralization (TZM.bl assay, limit of detection 1000ug/mL), Tier 1 neutralization of MN.3 and SF162 strains (TZM.bl assay), and gp120 binding (ELISA).

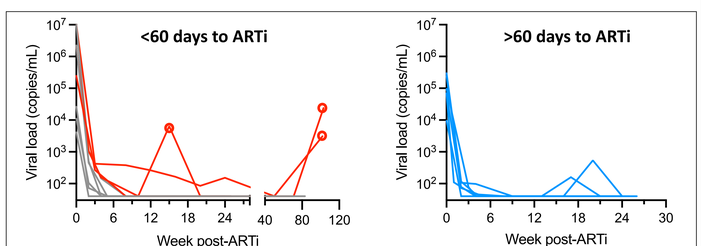


Figure 1: Viral load after ARTi. Participants initiating ART <60 days after EDDI (estimated date of infection) on left (n=9), and >60 days after EDDI on right (n=6). 3/9 participants in the <60 day group experienced viremia >500 copies/mL after suppression of viremia (participants in red, open circle denotes viremic timepoint).

Autologous neutralizing antibodies develop *only after a threshold of viral exposure* is surpassed prior to or following ART initiation

- Initiation of ART in first 60 days prevented autologous neutralizing antibody (anAb) development, *except in* cases with viremia after viral suppression
- Initiation of ART after 60 days of viremia allowed for anAb development
- anAb responses persist and mature over time on continued ART

RESULTS

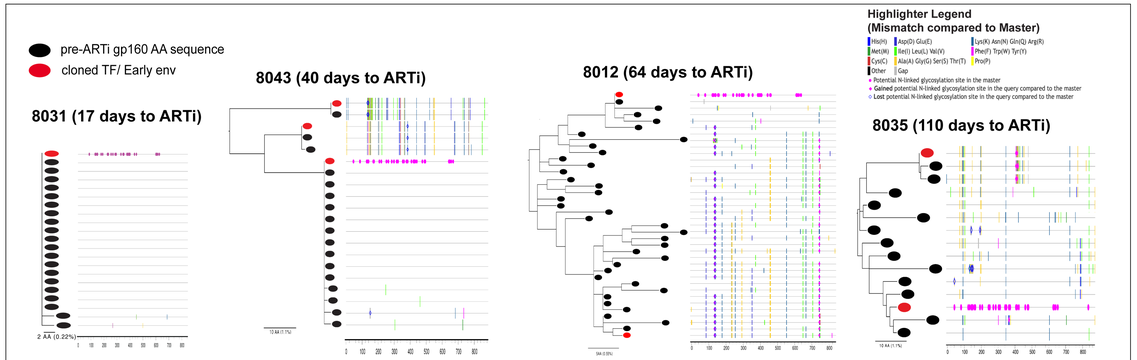


Figure 2: SGA and TF/Early virus identification. By SGA (n=311 total, median=22/participant timepoint), TF env was identified in participants initiating ART < 60 days after estimated infection date (ex. left, 8031 and 8043) and early virus was identified in participants initiating ART > 60 days after EDDI (ex. right, 8012 and 8035).

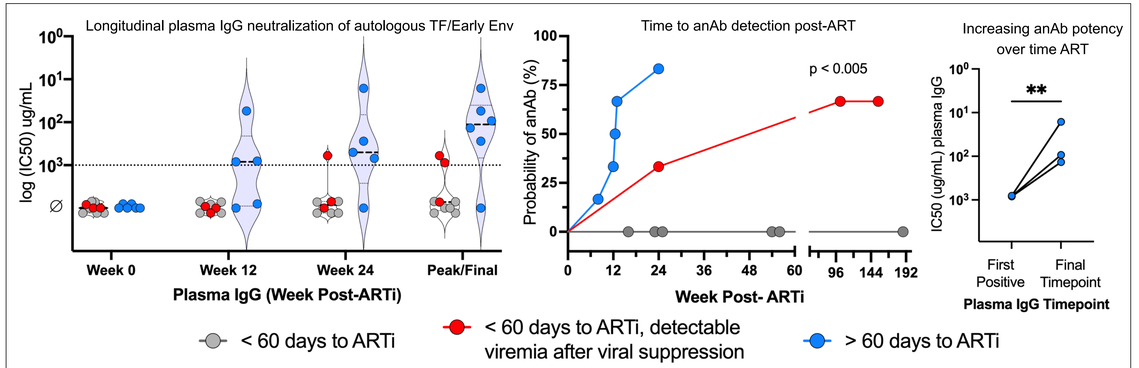


Figure 3: Autologous neutralization of pseudotyped TF/Early Virus by longitudinal post-ARTi plasma IgG. Among participants initiating ART < 60 days after EDDI, 2/9 developed anAb after ARTi (8028, IC50=598 ug/mL at week 24; and 8043, IC50 = 874 at week 102) - both of whom experienced detectable viremia after viral suppression on ART. Among participants initiating ART > 60 days after EDDI, 5/6 developed anAb after ARTi; peak IC50 occurred at latest timepoint (peak IC50 range 276-16.2 ug/mL, median 93 ug/mL). Left: autologous IC50 values at various post-ARTi timepoints, negatives represented below dotted line. Middle: log-rank test of time to detectable anAb ($p<0.005$, Mantel-Cox). Right: paired T test of autologous IC50 at first detected timepoint and final timepoint for the 3 participants with detectable IC50 prior to final timepoint ($p<0.005$).

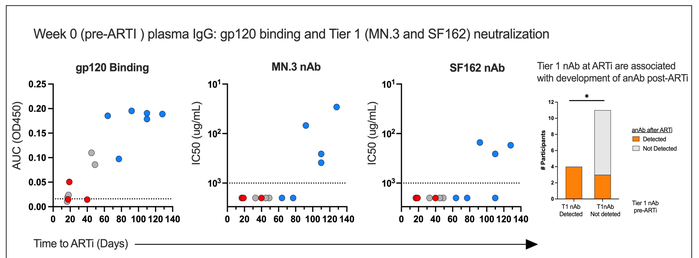


Figure 4: gp120 binding and Tier 1 neutralizing antibodies at ARTi. Left 3 panels: Gp120 binding and Tier 1 (MN.3, SF162) neutralizing antibodies (nAb) were assessed at pre-ARTi (week 0) plasma. Far right: Presence of Tier 1 nAb at ARTi was associated with development of anAb post-ARTi ($p < 0.05$, Fisher exact test), suggesting that anAb developing post-ARTi represent the maturation of pre-ARTi nAb responses.

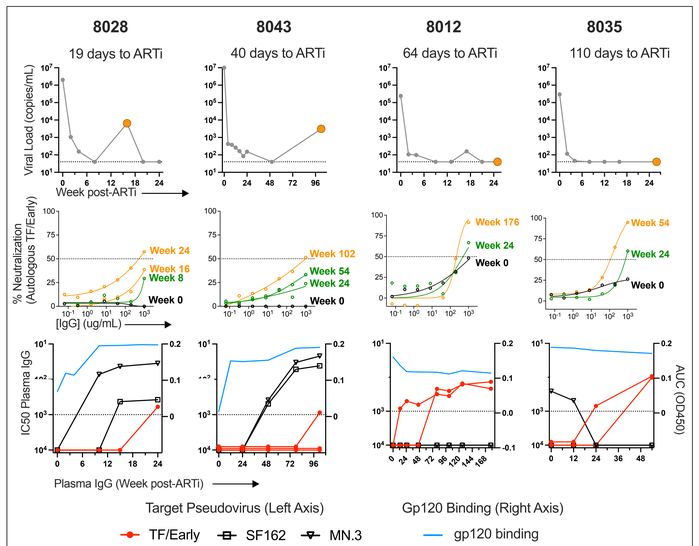


Figure 5: Kinetics of antibody development in selected participants. Viral load (top), autologous neutralization by TZM.bl assay from selected plasma IgG timepoints (middle), and overlayed longitudinal autologous neutralization, gp120 binding, and Tier 1 neutralization (bottom) from participants 8028, 8043, 8012, and 8035.

CONCLUSIONS AND IMPLICATIONS

- Results suggest that anAbs develop after ARTi in participants who experience a threshold of exposure to virus, resulting from sufficient period of viremia prior to ARTi or subsequent viremia following ARTi
- anAb continue to develop post-ARTi and are associated with pre-existing gp120 binding and Tier 1 neutralizing responses
- Initiating ART in acute HIV prevents development of neutralizing antibody responses, however strategies which increase antigen exposure on ART may allow for boosting of weak nAb responses