Early Therapy of Youth with Acute/Recent HIV: Effect on HIV DNA & Antibody (ATN 147)

Adolescent Medicine Trials Network (ATN) for HIV/AIDS Interventions, Project CARES Team

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BACKGROUND

Recent studies in adults indicate early potent antiretrovirals (ARV) in acute HIV infection may reduce viral reservoir size, and potentially result in better long- term viral control. There is limited data, however, on the large population of HIV-infected high-risk youth. We hypothesize that the decay of HIV reservoirs and accompanying immune responses are different in youth who have an active thymus and are treated early with potent ARV.

As part of a clinical trial, ATN 147, which identified acutely or recently HIV-infected youth (12-24 years) in multiple sites at Los Angeles and New Orleans, we assessed HIV viral load by HIV RNA PCR, viral reservoirs by DNA digital droplet PCR (ddPCR) and HIV antibody at baseline and sequentially for 12-24 months.

Over 1,500 recruited high risk HIV sero-negative youth were also followed prospectively for high risk exposure, seroconversion or symptoms of acute HIV and if positive they enrolled into the acute study and were offered immediate initiation of potent ART.

METHODS

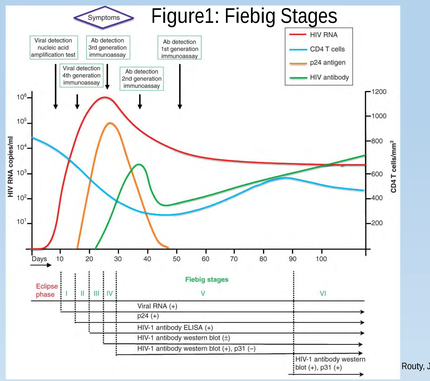
ATN 147 overall enrolled 87 high-risk youth at multiple sites in Los Angeles and New Orleans with newly diagnosed HIV infection, *all treatment naive*. HIV-1 diagnoses was done via point-of-care assays (Alere, Gene Xpert) with participants immediately enrolled into Study 1 to begin potent 4 drug cART. Most participants received Genvoya as a single pill or equivalent (4 drugs) with an average time to treatment of 3.6 days (range 0-28 days) along with coaching for adherence to medications and importance of follow up. Blood samples were collected at baseline, 1 & 2 weeks, 1, 2, 4, 8, 12, 18 and 24 month.

HIV antibody was assessed at baseline to determine Fiebig staging (Biorad 4th generation HIV-1 western blot kit). Study 1 participants were categorized as acute infection (AI) fiebig stage I-V (HIV p31 band absent) or recent infection (RI) fiebig stage VI (HIV p31 band present) (see figure 1). 32 had acute infection Fiebig stage I-V (37%) and 55 recent infection Fiebig stage VI (63%). HIV western blot was repeated at 12 and 24 months post treatment. Presence and intensity of major HIV bands (gp160, gp120, gp41 & p24) compared to controls were used to determine positive, indeterminate or negative interpretations by manufacturer's criteria.

CD4/CD8 T cell counts and plasma HIV RNA (LOD<20cp/ml) were measured sequentially. Youth were considered complete virological responders (CR) if plasma HIV RNA became undetectable (UD) and sustained at <20cp/ml; partial responders (PR) if HIV RNA became UD with minor blips; non-responder (NR) if HIV RNA never reached UD.

HIV DNA was measured by digital droplet (ddPCR) on PBMC with primers/probe SR1/661/ZXF (LOD<4cp/10^6).

Figure1: Fiebig Stages



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VIROLOGICAL RESPONSE- HIV RNA and DNA (ddPCR) over 12 months FU

Figure 2: Complete Responders
(HIV RNA drops <20 cp/mL and remains undetectable)

HIV RNA (cp/mL)
HIV ddPCR (cp/10^6)

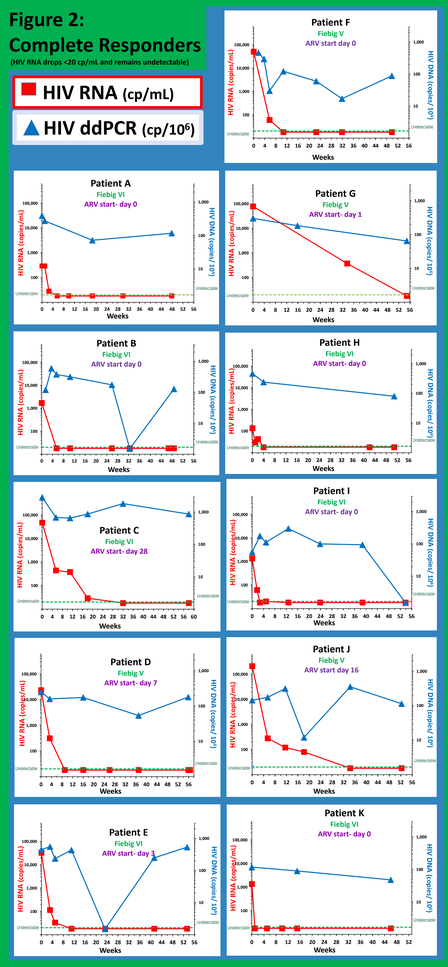


Figure 3: Partial Responders
(HIV RNA drops below undetectable but rebounds above 20cp/mL)

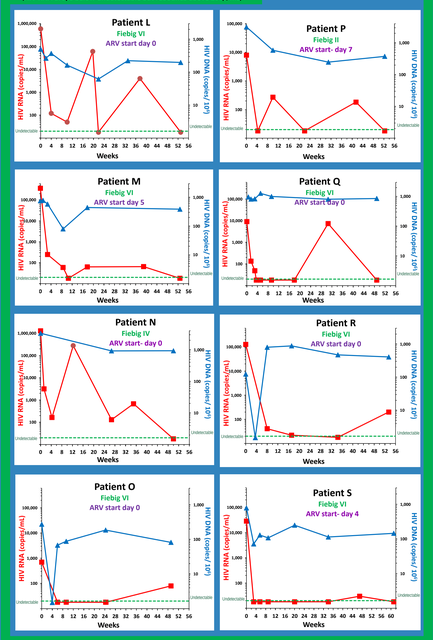


Figure 4: Non-Responder
(HIV RNA does not drop to undetectable)

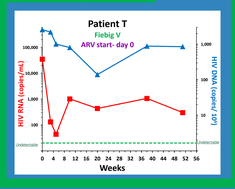


Figure 5: HIV DNA ddPCR entry vs 12mo

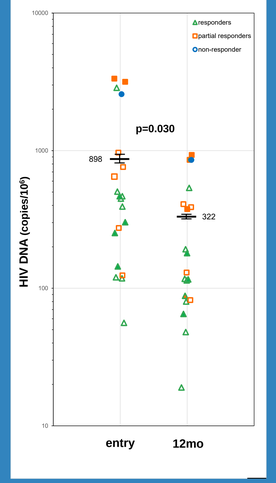
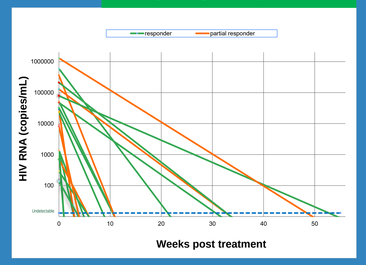


Figure 6: plasma HIV RNA time to undetectable (<20cps/mL)



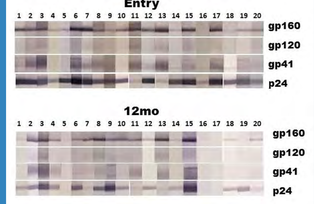
IMMUNOLOGICAL RESPONSE

HIV antibody

Table 2: Western Blot Interpretations

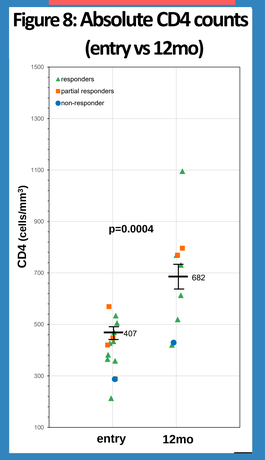
	Positive	Indeterminate
Entry	15	5
12mo	6	14

Figure 7: Western Blots major HIV bands



CD4 counts

Figure 8: Absolute CD4 counts (entry vs 12mo)



RESULTS: PRELIMINARY

Table 1: Population		Total n=87	Subgroup (12mo FU) n=20
Age		21.0	20.9
Race	Black	49	12
	Other	38	8
Sex	Male	85	20
	Female	2	0
Sexual Preference	MSM	76	16
	Other	11	4
Acute		32	7
Seroconversions		19	1

A total of 20 (all male) with mean age 20.9 yrs reached ≥ 12 mos. of follow-up to date. The majority were black MSM and one was a seroconverter and 7/20 (29%) were acute (table 1). Eleven were CR, 8 PR and 1 NR with significant drops in HIV RNA viral load for responders and partial responders (figures 2,3,4). Mean HIV RNA overall at baseline was 158,583 cps/mL dropping to 68 cps/mL at 12 months (p=0.04). Mean HIV RNA of acutes was 242,324 cps/mL vs recents 92,406 cps/mL. The mean time to undetectable plasma HIV RNA was 16 wks. (range 3-55) in 19/20 participants (figure 6).

As seen in figure 5, overall mean HIV DNA ddPCR at baseline (n=20) was 898 copies/10^6 (SEM=246) and significantly decreased to 322 copies/10^6 (SEM=71) at 12 months (p=0.03). HIV DNA levels remained constant or increased in 3/20; 17 had a decrease and 1 achieved very low levels (<4 cp/10^6) at 12 months. There was an average 72% drop of HIV DNA in the 7 acute vs 27% drop in recent.

Table 2, HIV antibody by Western blot showed a decrease in bands resulting in indeterminate results in 14/20 at 12 months post treatment. As seen in figure 6, intensities of HIV bands lessened from entry to 12 mos.

Figure 8, Mean absolute CD4 T cell counts at baseline (n=20) were 407 cells/mm^3 (SEM=109) and significantly increased to 682 cells/mm (SEM=227) at 12 months (p=0.0004).

CONCLUSIONS

- Results indicate that youth who begin potent cART early in acute/recent infection have **suppressed viremia**, and **significantly lower viral reservoirs** (HIV DNA ddPCR). Early cART can also **reduce HIV antibodies** and increase CD4 T cells in those with persistent virus suppression.
- Early treatment could lead to an overall lessened viral exposure over time potentially mitigating chronic immune dysfunction with a more favorable long term disease prognosis than those who initiate ARV later.
- **Identification, recruitment, treatment and follow up of high risk U.S. youth with acute/recent HIV is feasible.** Youth with lower levels of HIV viral reservoirs are a key target for future evaluation of CURE/remission strategies including therapeutic vaccination.

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