Effect of Tamoxifen on Vorinostat-induced HIV RNA Expression in Women on ART (ACTG A5366): The MOXIE Trial

Abstract: 333

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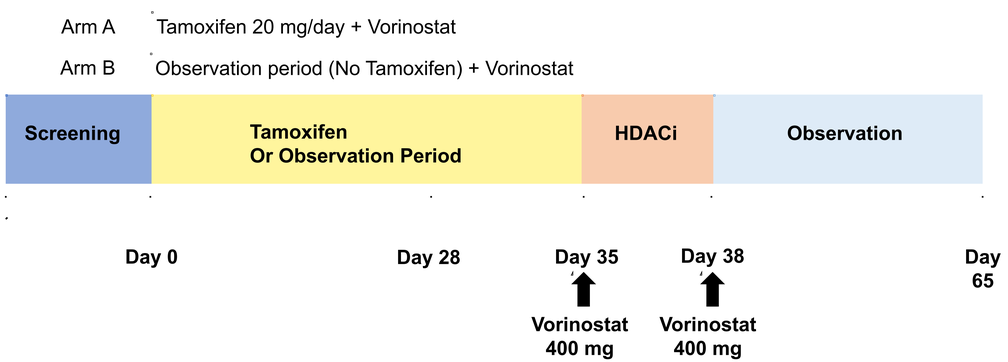
BACKGROUND

HIV reservoirs differ between men and women but few women have been enrolled in HIV cure trials to date[1,2]. *In vitro* and *ex vivo* data have identified a suppressive role for the estrogen receptor in HIV transcriptional control[3]. ACTG A5366 investigated whether the selective estrogen receptor modulator tamoxifen enhances HIV transcription *in vivo* after vorinostat exposure.



METHODS

Postmenopausal women with HIV suppression for >1 year and continuous ART for ≥2 years were randomized 2:1 to 5 weeks of tamoxifen (Arm A VOR+TAMOX) vs observation (Arm B VOR); both groups received 2 doses of vorinostat 400 mg separated by 72 hours on trial days 35 and 38. Primary outcomes were (1) safety in all women who received any study drug (N=30) and (2) change in HIV RNA expression from baseline to 5 hours after second vorinostat dose (day 38) in those receiving full study treatment, the efficacy population (N=27).

Total HIV DNA and unspliced cell-associated RNA (CA-RNA) were measured in $5x10^6$ CD4 T cells by qPCR. HIV RNA was also measured in a separate assay, using 10^6 spliced HIV envelope transcripts measured in 10^6 resting memory CD4 cells (EDITS assay[3]). Single copy assay (SCA) of plasma viremia was performed. Histone H4 acetylation used a H4K5, 8, 12, and 16 immunoassay in which thawed peripheral blood mononuclear cell-derived cell lysates were added to an ELISA using antiH4 monoclonal antibody[4,5]. 17beta estradiol levels were measured with LC-MS. Arms were compared by t-tests of log-transformed virology measures, after imputing half an analytic lower limit for results below limit. Sensitivity analyses used longitudinal censored-data methods, applied to result-specific lower limits.

TABLE 1

	Overall	Arm A (VOR+TAMOX)	Arm B (VOR)
Sex/gender (Female/Female) (number (%))	31 (100)	21 (100)	10 (100)
Age (median [Q1,Q3])	57 (53-60)	57 (54-61)	55 (51-59)
Race (number (%))			
American Indian or Alaskan Native	1 (3)	1 (5)	0 (0)
Black or African American	18 (58)	11 (52)	7 (70)
White	12 (39)	8 (38)	3 (30)
Ethnicity (number (%))			
Hispanic/Latino	6 (19)	4 (19)	2 (20)
Not Hispanic/Latino	25 (81)	17 (81)	8 (80)
Years since ART start (median [Q1,Q3])	7.5 (2.9-13.9)	6.1 (2.4-13.9)	9.4 (5.9-12.2)
Nadir CD4 (cells/mm³) (median [Q1,Q3])	232 (46-363)	232 (10-363)	261 (80-402)
Screening CD4 (cells/mm³) (median [Q1,Q3])	688 (536-854)	688 (536-773)	722 (566-1106)

FIGURE 2

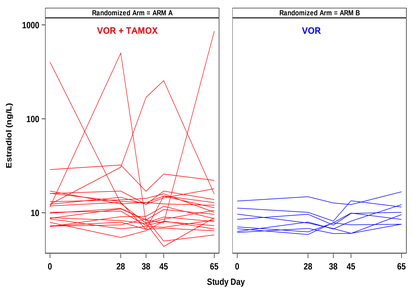


Figure 2. 17beta estradiol levels showed minimal variation over the study.

FIGURE 1

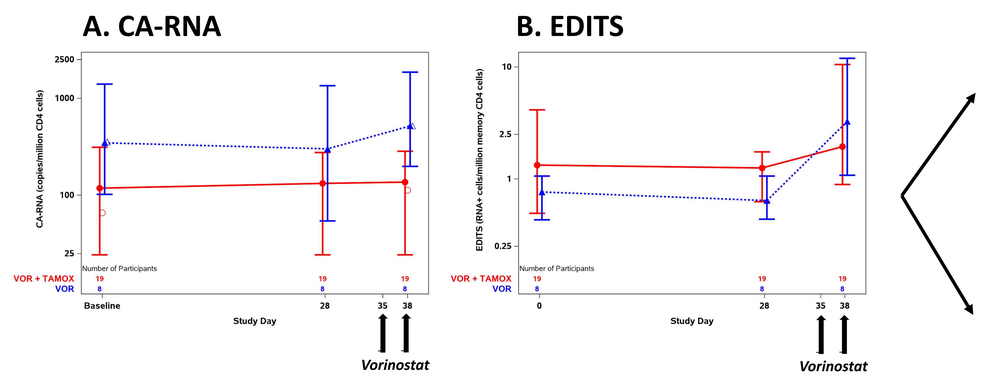


Figure 1. Induction of HIV transcription as measured by (A) CA-RNA from isolated CD4 cells and (B) EDITS from isolated resting CD4 cells. There is no difference in the induction of HIV RNA between the two study arms. Filled symbols are mean and bars indicate Q1,Q3. Open symbols on (A) CA-RNA indicate the mean values when using result-specific lower limits of quantification. (C) Pooling arms, induction of HIV RNA as measured by EDITS was stratified by H4 acetylation changes from day 28 to day 38. Box plots indicate mean and Q1,Q3 for each group.

RESULTS

- 31 women enrolled in 3 months; characteristics are summarized in Table 1
- No Grade ≥ 3 adverse events related to study drugs were seen
- The efficacy population comprised 27 women (19 Arm A VOR+TAMOX, 8 Arm B VOR). There was no difference between the groups in the change in HIV expression by CA-RNA (mean fold change: Arm A VOR+TAMOX 1.2, Arm B VOR 1.5, p=0.6) or in EDITS (mean fold change Arm A VOR+TAMOX 1.5, Arm B VOR 4.3, p=0.12). (Figure 1A, B)
- Following vorinostat, 18 participants had increased histone acetylation; in these women, HIV expression by EDITS also increased (mean fold increase: 2.8). (Figure1C)
- There were no changes in HIV DNA or SCA
- Targeted plasma concentrations of tamoxifen and vorinostat were achieved
- Minimal variation in estradiol concentrations were observed among participants (Figure 2)

ACKNOWLEDGEMENTS

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CONCLUSIONS

In post-menopausal women receiving vorinostat, ESR1 antagonism with tamoxifen was not associated with enhanced change in the magnitude of HIV RNA induction by qPCR or EDITS. Induction of HIV RNA after vorinostat by the EDITS assay was primarily seen in women with increases in histone acetylation. Increase in H4 acetylation was only observed in 67% of trial participants; this may have limited the ability to detect an effect of tamoxifen. This clinical trial, the first to study HIV latency reversal exclusively in women, was rapidly enrolled and completed, supporting the feasibility of future efforts to investigate sex-specific features of the HIV reservoir.

FUNDING

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