

# Valganciclovir Reduces CD8+ T Cell Activation among HIV-infected Patients with Suboptimal CD4+ T cell Recovery During Antiretroviral Therapy

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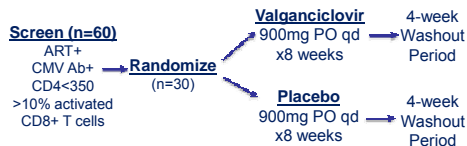
## Background

- HIV infection results in a massive expansion of CD38+HLA-DR+ CD8+ T cells, which fails to completely normalize during antiretroviral therapy (ART).
- While the precise function of these cells remains unclear, they have been a consistent marker of generalized immune activation and/or dysfunction in HIV infection, predicting earlier mortality in untreated disease and poor CD4+ T cell recovery during suppressive ART.
- The causes of persistent immune activation despite ART are unclear, but may include persistent release of HIV from latently-infected cells, microbial translocation, or other chronic co-infections.
- We hypothesized that asymptomatic cytomegalovirus (CMV) co-infection would be a major determinant of immune activation in this setting as it is:
  - Highly prevalent in HIV-infected individuals (>90%)
  - Results in a dramatic expansion of CMV-specific T cells (~10% of the entire circulating memory T cell pool in asymptomatic HIV-adults).
  - Replicates more in the setting of HIV-associated immunodeficiency.

## Methods

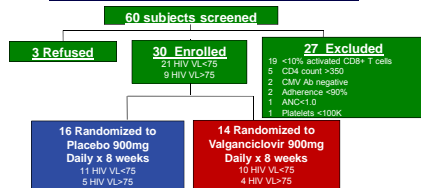
- We performed a single-center randomized controlled trial of valganciclovir among HIV-infected individuals with sub-optimal CD4 recovery during ART.
- Valganciclovir is an orally bioavailable 2'-deoxyguanosine analog commonly used to treat CMV end-organ disease and is a potent inhibitor of CMV and other herpesvirus replication.
- Inclusion Criteria:** CMV-seropositive, HIV+ adults on stable ART regimen for ≥6 months and with CD4+ T cell counts <350 cells/mm<sup>3</sup> for ≥1 year were eligible.
- Exclusion Criteria:** <90% adherence to ART in last 30 days, any serious illness in last 3 months, active CMV end-organ disease requiring treatment, receipt of ganciclovir, valganciclovir or any concurrent nephrotoxic, immunosuppressive, or immunomodulatory drug in the previous 30 days, pregnancy, breastfeeding, or any of these laboratory abnormalities: abs neutrophil count <1,000 cells/mm<sup>3</sup>, platelet count <100,000 cells/mm<sup>3</sup>, hemoglobin <8mg/dL, estimated Cr clearance <50 mL/minute. To enrich the study sample for those with high T cell activation, those with <10% activated CD8+ T cells were excluded.
- Randomization:** block randomization stratified by plasma HIV RNA level (< or >75 c/ml)
- Intervention:** Valganciclovir 900mg PO daily vs. Placebo x 8 weeks
- 1<sup>st</sup> Outcome:** Change in %activated (CD38+HLA-DR+) CD8+ T cells at week 8.
- T cell activation assessed with multi-color flow cytometry on cryopreserved PBMC at end of study (screening levels were performed on fresh specimens).
- CMV, HHV-6, HHV-8, and EBV DNA levels were assessed in the laboratory of Larry Corey (UW) in cryopreserved saliva, plasma, and semen.
- Soluble markers of inflammation (IL-6, CRP) and coagulation (d-Dimer) were assessed on cryopreserved plasma in the laboratory of Russell Tracy.
- Sample Size:** With a std deviation of 5% in the week 8 Δ in % activated CD8+ T cells, α=0.05, we would have 80% power to detect a difference between groups as small as 5.5% with 13 subjects per arm. Anticipating premature discontinuations, we planned to enroll 15 per arm.

## Valganciclovir Trial Schematic



## Results

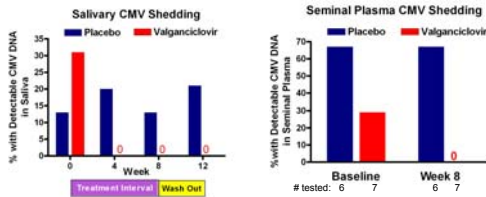
### Screening and Enrollment Summary



### Baseline Characteristics of Study Subjects

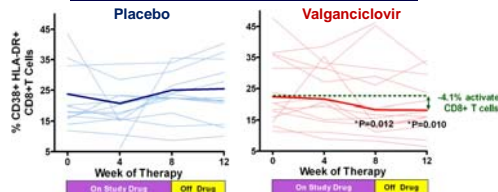
Characteristic	Placebo	Valganciclovir
	N=16 Median (IQR)	N=14 Median (IQR)
Age, years	50 (44-59)	48 (43-55)
Male gender, No. (%)	16 (100)	12 (86)
Months on current ART regimen	27 (17-35)	28 (16-40)
CD4+ T cell count, cells/mm <sup>3</sup>	187 (108-218)	207 (176-249)
Plasma HIV RNA level, No. (%)		
<75 copies/ml	11 (69)	10 (71)
>75 copies/ml	5 (31)	4 (29)
CD4 count nadir, cells/mm <sup>3</sup>	64 (20-114)	18 (8 to 54)

### Durable Suppression of CMV DNA with Valganciclovir

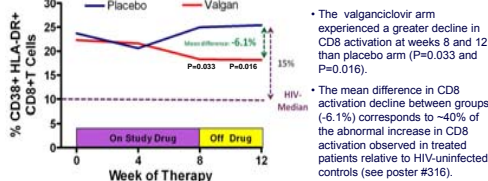


- CMV DNA levels were measured by PCR (LLD 150 copies/ml) every 4 weeks in plasma and saliva, and at baseline and week 8 in seminal plasma.
- CMV DNA was detectable in saliva, plasma, or seminal plasma at baseline in 7/16 (44%) placebo-treated subjects and 5/14 (36%) valganciclovir-treated subjects.
- CMV DNA could no longer be detected in any fluid at any timepoint after baseline (even after 4-week washout phase) in the valganciclovir group, but continued to be detectable in 44% of placebo participants (P=0.007).
- EBV DNA levels also declined through week 8, but rebounded to near baseline levels by week 12. Effects of valganciclovir on HHV-6 and HHV-8 shedding were not appreciable.

### Valganciclovir Decreases CD8 Activation



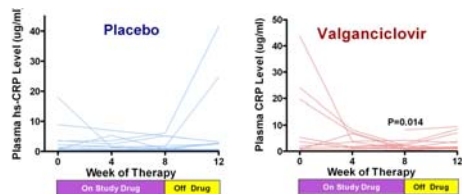
- Changes in CD8 activation were assessed with generalized estimating equations, dark lines representing estimated mean changes.
- There was no evidence for a change in CD8 activation in the placebo arm.
- However, CD8 activation declined significantly in the valganciclovir arm at weeks 8 (P=0.012) and 12 (P=0.010). The mean decline of 4.1% at week 12 represents a 20% relative reduction from the median baseline level.
- Even when restricting to those with plasma HIV RNA levels <75, valganciclovir significantly reduced CD8 activation levels at weeks 8 (P=0.044) and 12 (P=0.006).



- The valganciclovir arm experienced a greater decline in CD8 activation at weeks 8 and 12 than placebo arm (P=0.033 and P=0.016).
- The mean difference in CD8 activation decline between groups (-6.1%) corresponds to ~40% of the abnormal increase in CD8 activation observed in treated patients relative to HIV-uninfected controls (see poster #316).

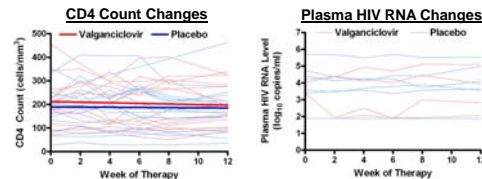
\*P for difference in the change from week 0 between valganciclovir- and placebo-treated groups

### Valganciclovir Appears to Decrease hs-CRP Levels



- While there was no evidence for a change in hs-CRP levels in the placebo arm, hs-CRP levels appeared to decline in the valganciclovir arm by week 8 (P=0.014).
- However, the difference between arms in week 8 CRP changes was not significant (P=0.20).
- There was also no evidence for a change in plasma IL-6, d-Dimer, sCD14, or cytokine C levels in either group, but power is limited given high levels of within-subject variability.

### No Evidence For CD4 Count or Plasma HIV RNA Changes



- There was no evidence for a change in either CD4+ T cell counts or plasma HIV RNA levels in either group during the observation period.

### No Evidence For Treatment-related Toxicity

- There was only one adverse event in the trial (a placebo recipient who had a congestive heart failure exacerbation prior to the week 4 visit).
- While only 14 subjects received valganciclovir for just 8 weeks, we observed no evidence of treatment-related toxicity.
- Specifically, we observed no evidence of changes in hemoglobin levels, absolute neutrophil counts, platelet counts, or creatinine clearance, each measured biweekly.

## Conclusions / Implications

- Valganciclovir durably suppresses CMV replication and CD8+ T cell activation in HIV-infected patients with poor CD4 recovery during ART.
- This reduction in CD8 activation does not appear to be mediated by a direct effect on HIV replication, but appears to be the result of reductions in CMV (or other herpesvirus) replication.
- Thus, CMV (and possibly other herpesviruses) appears to be a major determinant of CD8+ T cell activation during antiretroviral therapy.

- Given the potential impact of inflammation and immune activation on clinical outcomes (see poster 306), and the potential role of CMV in cardiovascular disease, T cell senescence, and aging, strategies to reduce CMV replication in HIV-infected individuals are worth pursuing in larger trials.

## Acknowledgements

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