The expansion of activated monocytes and activation of macrophages are consistently associated with HIV comorbidities, and activation persists despite ART in PLWH. In SIV infection models, we have shown that increased  monocyte turnover, measured by BrdU monocytes, is an early predictor of rapid progression to AIDS with severe CNS histopathology. The %BrdU monocytes correlates linearly with sCD163, the best biomarker of HIV comorbidities and a marker exclusively produced by monocytes macrophages. What monocytes and macrophages respond to is not defined, but proposed signals include residual SIV/HIV replication, secondary viral co-infection, and microbial translocation. Others have suggested that monocyte turnover increases to replenish macrophages that turn over with SIV infection. To test macrophage turnover as a signal for monocyte/macrophage activation, we used the CSF1R inhibitor BLZ-945 to ablate macrophages in ART-treated, SIV infected animals and measured total monocytes, monocyte subpopulations, and monocyte turnover (%brdu) during and after BLZ-945. During BLZ-945, found significantly lower numbers of vs. ART controls (p < 0.001), driven by decreases in the numbers of classical monocytes (p < 0.001) and nonclassical monocytes (p < 0.0001). The %BrdU monocytes did not change during treatment. After cessation of treatment, animals that had received ART+BLZ-945 had significantly greater rebound in total monocyte numbers (p < 0.001), driven by rebounding classical monocytes (p < 0.001) and nonclassical monocytes (p < 0.001). Kinetically, it appeared that classical monocytes emerged, followed by intermediate, then nonclassical monocytes in animals that received BLZ-945. The kinetics of rebound after BLZ-945 are consistent with replenishment of macrophages from classical monocytes, which differentiate into intermediate then nonclassical monocytes in the blood. Interestingly, the %BrdU monocytes remained non-detectable after treatment cessation in ART+BLZ animals, suggesting that release of existing monocyte reservoirs (e.g. spleen) contributed to monocyte rebound rather than increased turnover. These data suggest that macrophage turnover during ART does not contribute to monocyte/macrophage activation.

**Total monocyte number**

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A graph of lines and dots

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**Classical monocytes, absolute**

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A graph of lines and dots

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**Intermediate monocytes, absolute**A graph of a graph showing the number of lines

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**Nonclassical monocytes, absolute**

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**%BrdU**

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