**HIV-1** stimulates Human Monocytes to produce BAFF through Type I IFN and its secretion level shows sex-related differences

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**Background:** B-cell-activating factor (BAFF) is a TNF ligand superfamily protein mainly expressed by myeloid cells. It is a potent regulator of B-cell development and function; however its overexpression has been associated to several B-cell dysfunctions. BAFF has been found to be increased in HIV-1-infected patients, suggesting its possible role in the B-cell dysfunction observed during HIV-1 infection. The exact mechanism by which HIV-1 infection leads to increased BAFF secretion is still unknown. We hypothesized that HIV-1 could indirectly influence the functionality of B-cells by increasing BAFF production on monocytes, one of the main sources of this cytokine.

**Methods:** PBMC were isolated from blood samples of healthy, informed and consented volunteers (n=9; 5 men and 4 woman). Monocytes were purified from PBMC by magnetic separation and stimulated with fully infectious NL4-3(X4) or NL4-3Balenv(R5) virus, Poly I:C or IFN-α2a, or mock control for 24h. In some experiments, monocytes were pre-incubated with B18R receptor before stimulations to neutralize type I IFNs. BAFF protein secretion was evaluated using a commercial ELISA kit. Type I IFN activity was monitored using HEK293-blue IFN-α/β sensor cells in monocytes supernatants. Statistical differences were determined by one-way ANOVA and two-tailed student's t-test.

**Results:** BAFF secretion was significantly increased in supernatants from monocytes stimulated with NL4-3 and NL4-3Balenv compared to mock, similar results were obtained with Poly I:C or IFN-α2a after 24h (n=9; p< 0.05). Both viruses induced a strong type I IFN response (n=9; p< 0.05). Neutralization of secreted type I IFN with B18R receptor decreased BAFF secretion to basal levels in monocytes stimulated with X4 and R5 HIV-1, Poly I:C and IFN-α2a (n=6; p< 0.05). BAFF secretion was higher in monocytes obtained from women (n=4) than those obtained from men (n=5) (p< 0.05).

**Conclusion:** Our results demonstrate that fully infectious HIV-1 can directly increase BAFF secretion on human monocytes via type I IFN and its secretion levels are sex-dependant. This study will help to elucidate the mechanisms of BAFF augmentation and B-cell disorders observed in HIV patients. This information will be relevant for the future design of therapies that could restore the normal functionality of the B-cell compartment.