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Plasma Interferon-gamma-inducible protein-10 (IP-10) can be used to predict viral load in HIV-1 infected individuals

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To the Editors

Interferon-gamma (IFN-γ) inducible protein 10 (IP-10), also known as CXCL10, is a chemokine involved in both innate and acquired immune responses that directs T cells to sites of inflammation[1, 2]. Plasma IP-10 has been shown to correlate closely with inflammation, liver fibrosis and Hepatitis C virus infection[3], reflect HIV load in cerebral spinal fluid[4] and be a useful marker for early HIV disease progression[2, 5]. In addition, genital tract levels of IP-10 may reflect vaginal HIV load[6]. Herein we report on plasma IP-10 concentrations correlating with plasma viral load that can be used as a predictive marker of viral replication in HIV infected adults.

Plasma concentrations of IP-10 were evaluated by Luminex assay using a Bio-Plex Cytokine reagent kit (BIO RAD Laboratories, Hercules, CA, USA) in 51 HIV uninfected and 55 HIV-infected individuals, including 7 participants on antiretroviral (ARV) treatment. The median plasma IP-10 concentration in HIV-uninfected controls was 340 ng/ml (IQR: 249–468) and in all HIV-infected individuals (including those on ARV) there was a significantly higher concentration ($p<0.0001$ using Mann-Whitney) of 1160 ng/ml (IQR: 779–2088). There was also a significantly higher concentration of IP-10 when comparing HIV-uninfected and HIV-infected individuals receiving ARV (median: 778 ng/ml, IQR: 534–924, $p=0.0009$), although all on ARV were below the threshold of 400 RNA copies/ml. Relative to ARV-naïve HIV-infected individuals, the lower IP-10 concentration in patients receiving ARV is compatible with reduced inflammation upon viral suppression[7]. However, the finding that IP-10 is significantly higher in ARV-treated individuals, relative to uninfected controls, also suggests that inflammatory signals are not completely dampened and may reflect viral activity below the 400 copies/ml threshold. When grouping all HIV-infected individuals,

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there was a significant positive correlation ($p<0.0001$) between IP-10 and viral load ($r=0.71$, 95% CI: 0.52–0.84; Figure 1A), compatible with the close association between this chemokine and viral burden. We also measured IP-10 longitudinally in 25 of the 55 HIV-infected individuals over 9 months, where a significant correlation was observed between changes in both IP-10 and viral loads over time ($r=0.65$; $p=0.049$), accentuating the parallel course of viral load and IP-10. We used Receiver-Operating-Characteristic (ROC) curves to identify the possible predictive nature of IP-10. A significant area-under-the-curve (AUC) was noted when selecting viral loads above or below 5000 RNA copies/ml (Figure 1B, AUC=0.88; 95% CI: 0.77–0.98). This was also reflected when a threshold of 2000 RNA copies/ml was chosen (AUC of 0.888; 95% CI: 0.78–0.996, $p=0.0009$, not shown). Together, these data show the robust ability of plasma IP-10 concentrations to predict different levels of viremia with good sensitivity and specificity. Using a cross-over plot to precisely identify the point where specificity and sensitivity intersect, an IP-10 concentration of 900ng/ml could predict viral loads above and below 5000 RNA copies/ml (Figure 1C). These data highlight that IP-10 is a suitable host marker for predicting viral load and may potentially be used instead of the latter assay. IP-10 has also been proposed as a useful biomarker for sputum clearance in TB patients [8] and there are reports showing that IP-10 is useful to track disease progression in HIV infected individuals[5]. Our data would concur with this and we extend the analysis to show a direct association with in vivo viral replication, as has been similarly shown in Hepatitis C infection[9]. When we extended the analysis to CD4 counts, we identified that there was no association between IP-10 and CD4 count changes over time, and ROC curve analysis showed an AUC of 0.58, with no significant predictive capability. Thus, although plasma IP-10 is an excellent proxy and predictor for viremia, it is unrelated to CD4 numbers.

In summary, using ROC curve analysis, we have shown that IP-10 is a good predictor of viral load and is useful for tracking changes in viremia, including a response to ARV, and may be an alternative to the more costly viral load measurements. Whether there is a casual biological association between HIV and IP-10 is unclear, but we speculate that IP-10 is secreted as a direct effect of viral replication and activation of tumor necrosis factor alpha (TNF-α) and IFN-γ in host leukocytes[1]. As a result of this direct association, plasma IP-10 concentration can be used as an accurate proxy for viral load and could potentially be adapted to use as a point of care test. This is of great importance in a country such as South Africa, which has one of the largest ARV rollouts in the public health sector. Having a relatively quick colorimetric assay to measure this host-derived chemokine would obviate the need to send samples to regional or tertiary centres for viral load measurements.

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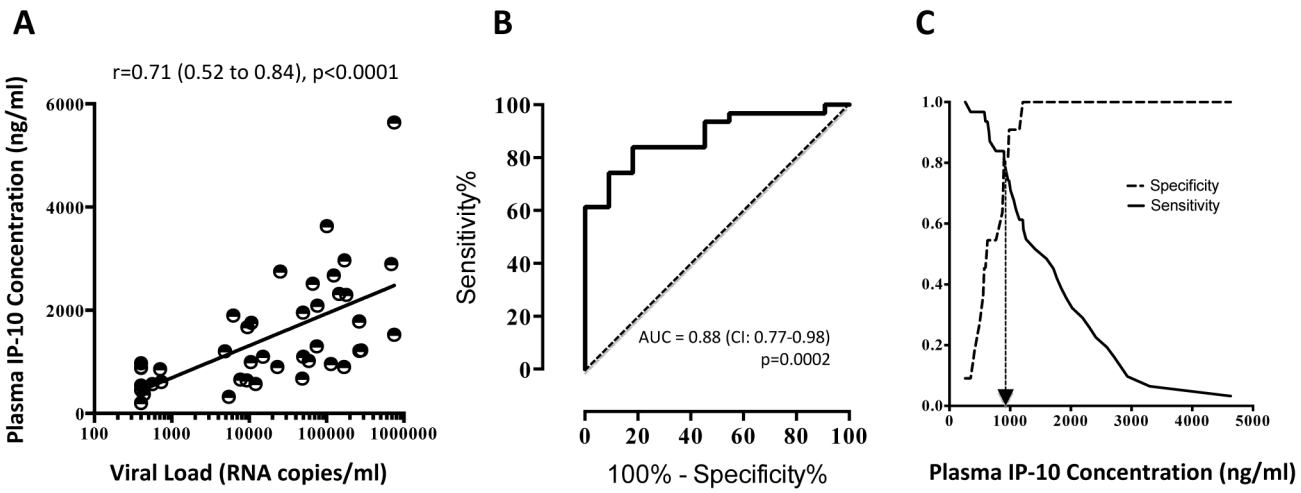

Figure 1. Plasma IP-10 concentrations correlate and predict viral load in HIV-1 infected individuals

A. Spearman Rank correlation between IP-10 concentrations and Log_{10} RNA copies/ml; B. Receiver-Operating-Characteristic curve showing significant area under the curve for IP-10 above and below 5000 copies/ml; C. Specificity/sensitivity cross-over plots showing the intercept at which the concentration of IP-10 is predictive (denoted by hashed arrow line).