

Striking elevations in systemic and mucosal cytokine and chemokine levels in acute HIV-1 infection

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Rationale for analysis of innate responses in acute HIV infection

Characterisation of the earliest virus-host interactions in HIV infection (at both mucosal and systemic sites) will help to give insight into the events that must be altered by vaccine-induced immune responses

Innate responses can be activated very rapidly after infection, and are important determinants of

- spread or containment of initial virus replication
- induction and regulation of adaptive responses

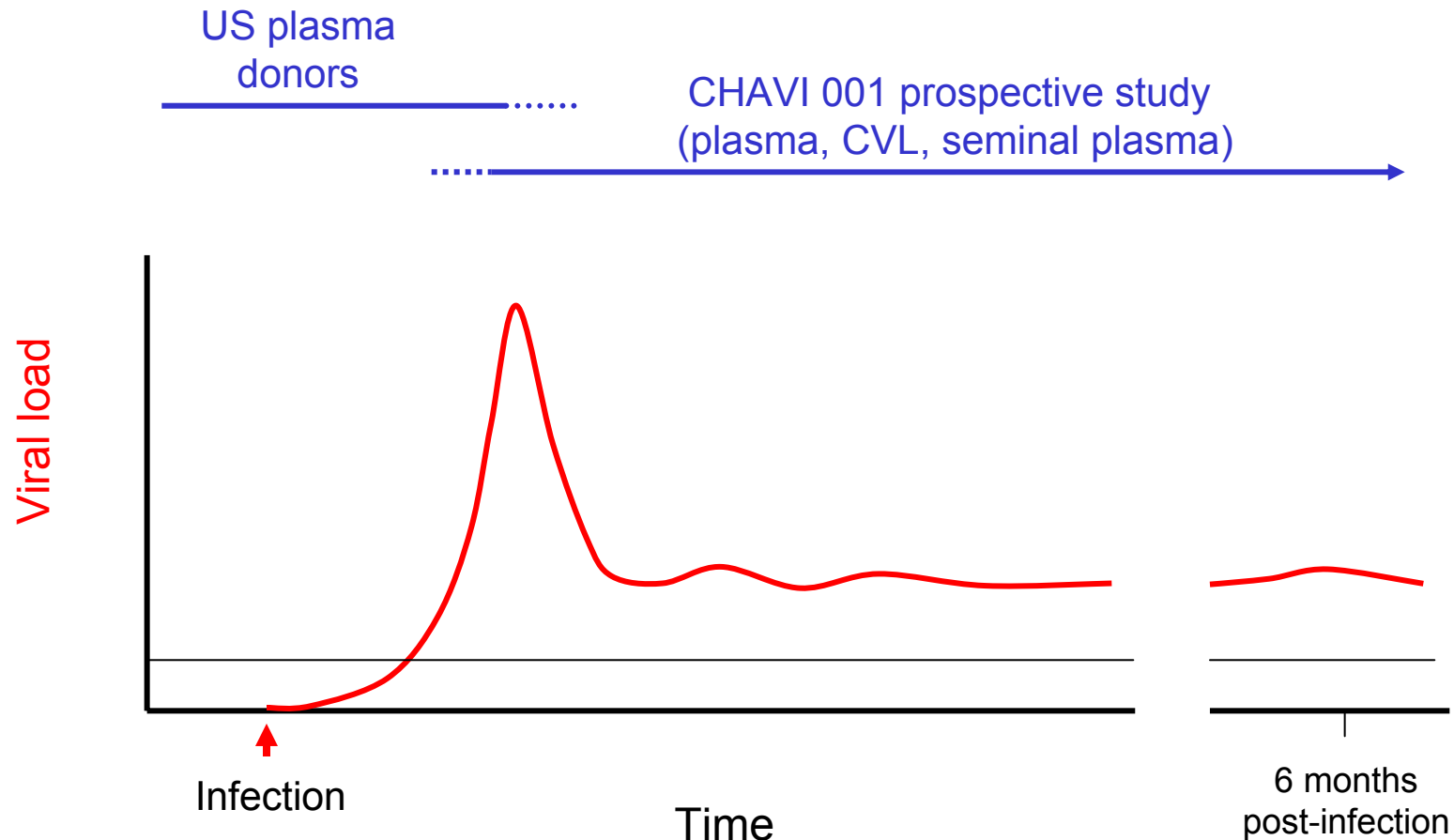
Questions being addressed

What are the nature and kinetics of the innate responses activated in acute HIV-1 infection: at mucosal sites? systemically?

What roles do these responses play in protection and pathogenesis in AHI?

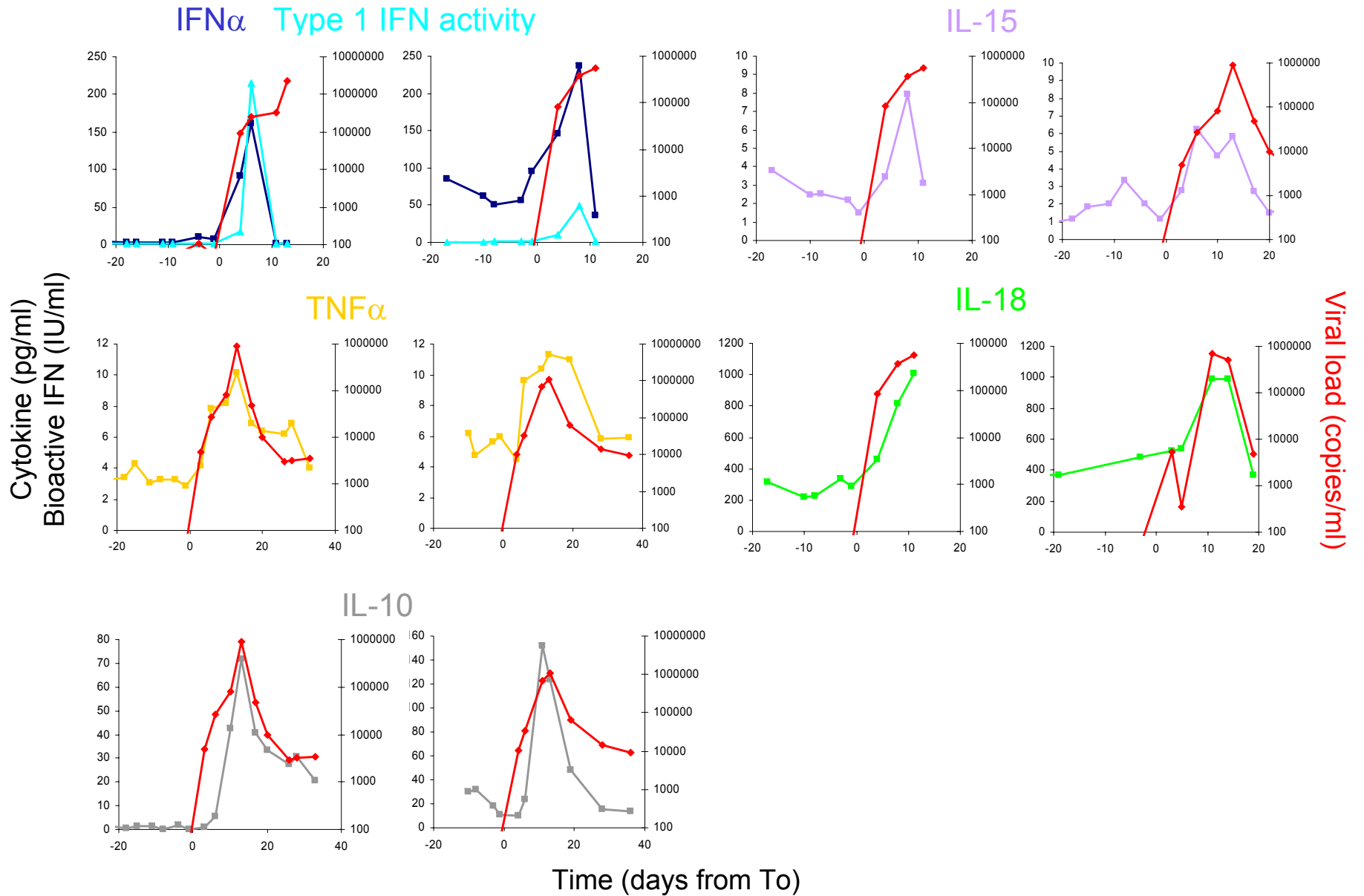
Could novel vaccination strategies be developed to confer protection via up- or down-modulation of components of the innate response activated following HIV infection?

Characterisation of the earliest innate immune responses in acute HIV-1 infection

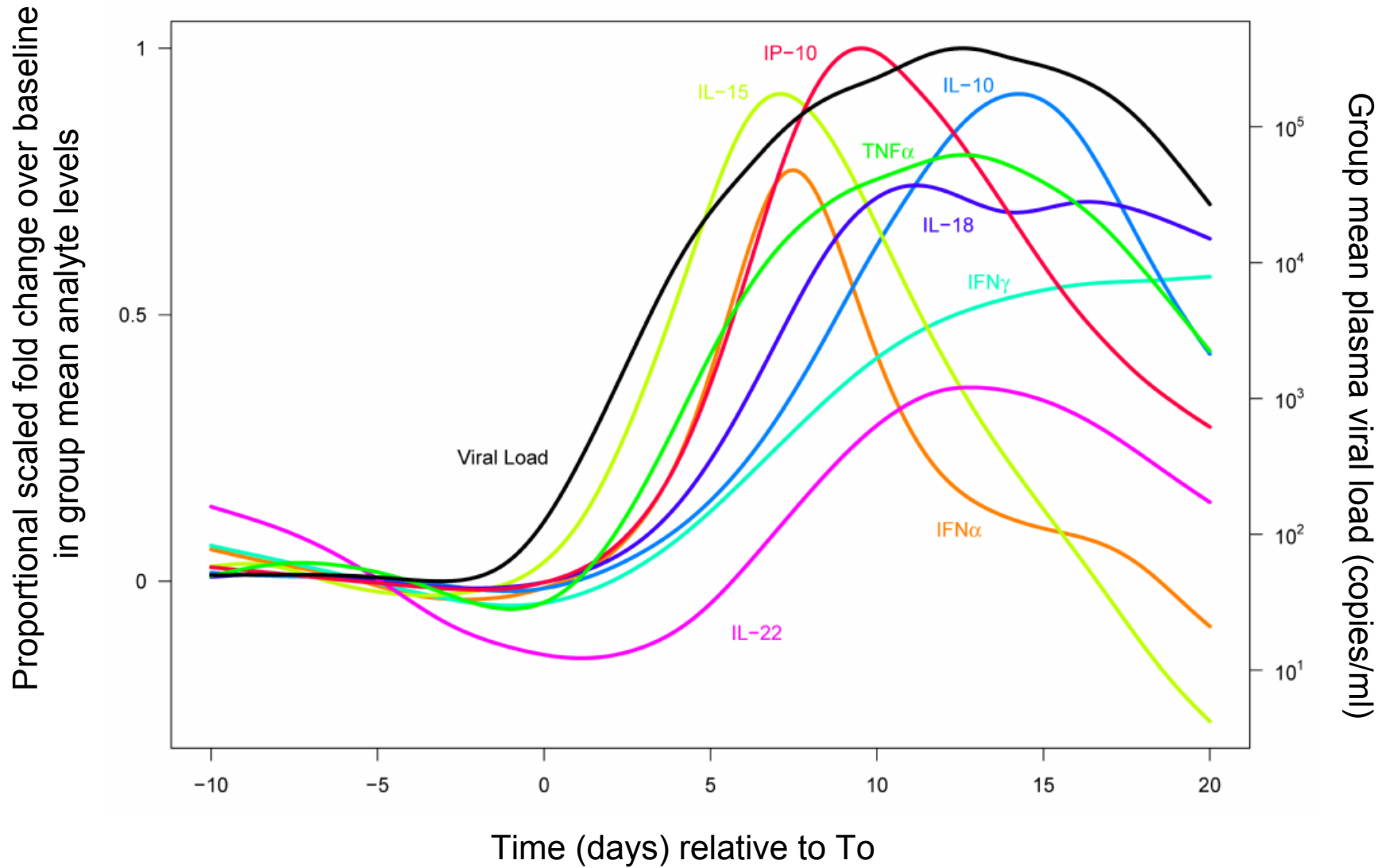


Cytokine and chemokine levels were measured by Luminex assay and ELISA in plasma, cervicovaginal lavage (CVL) and seminal plasma of HIV-1 infected subjects and uninfected controls

Examples of plasma cytokine elevations observed in acute HIV infection

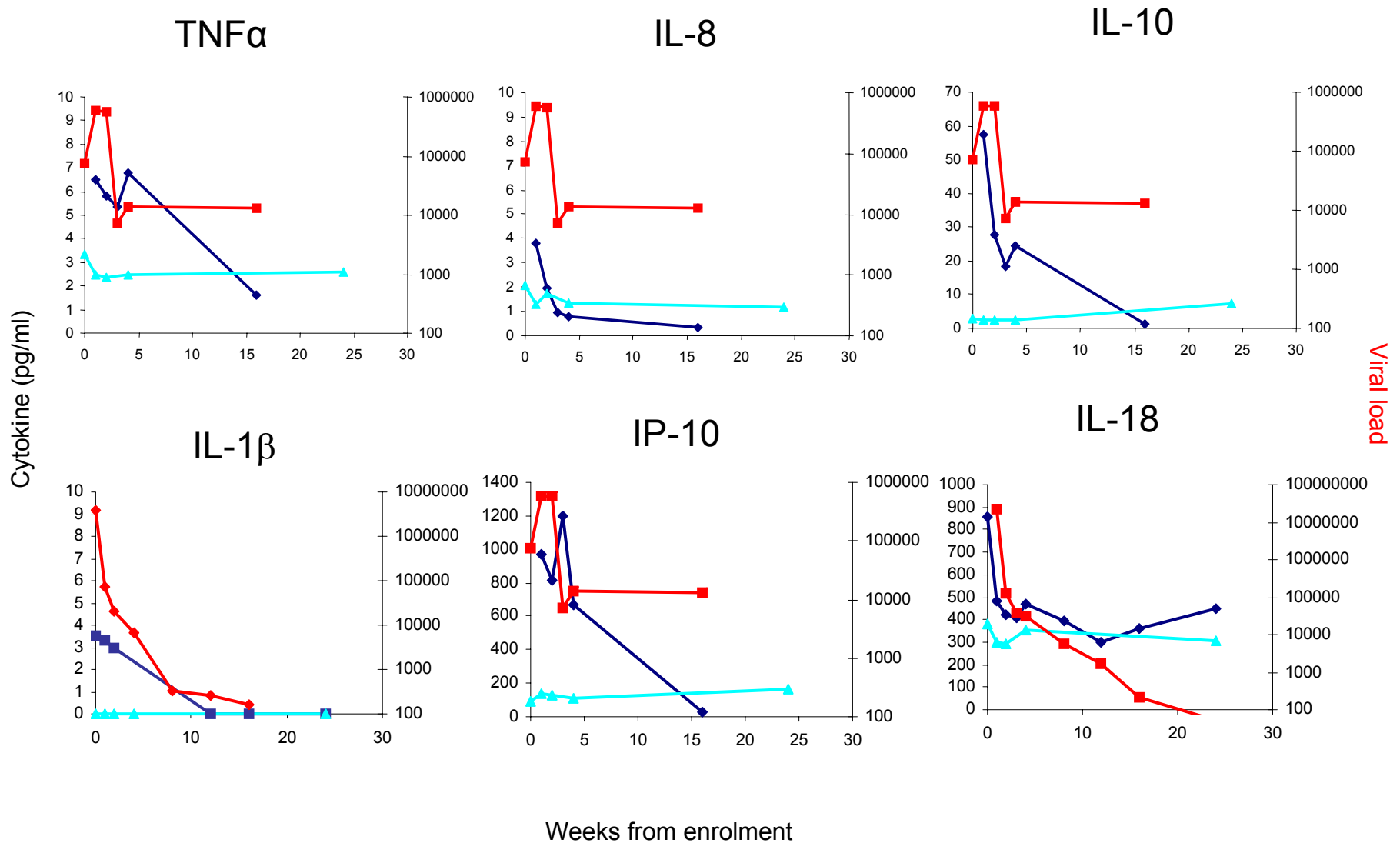


Summary of changes in plasma cytokine/chemokine levels in AHI



Plasma levels of most analytes rapidly return to baseline with declining viral load

◆ Acute HIV subject ▲ HIV negative subject



Analysis of cytokine/chemokine levels in mucosal fluids in AHI: CVL

Aim: To gain insight into the nature and kinetics of innate responses at the site of initial infection and their impact on subsequent events in HIV infection

Cytokine and chemokine levels analysed in CVL samples and matched blood plasma samples from female AHI subjects and HIV-negative control subjects from CHAVI 001

Multiple cytokines/chemokines were found to be transiently elevated in CVL during AHI in many of the HIV-infected subjects studied

Transient elevations in some of these analytes were also observed in CVL samples from occasional HIV-seronegative control subjects (all of whom had STIs)

Elevations in CVL cytokine/chemokine levels in AHI

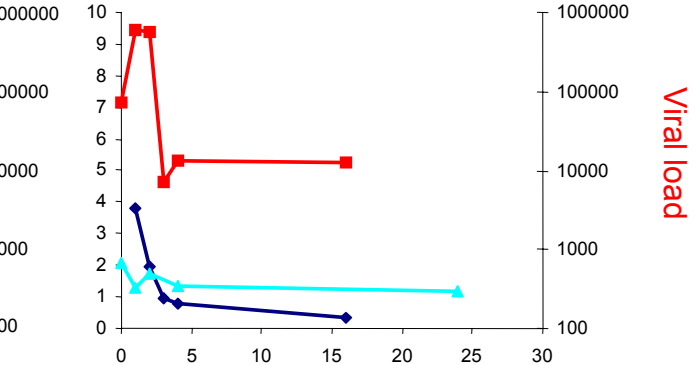
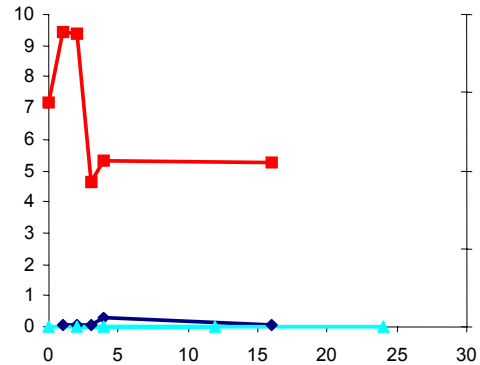
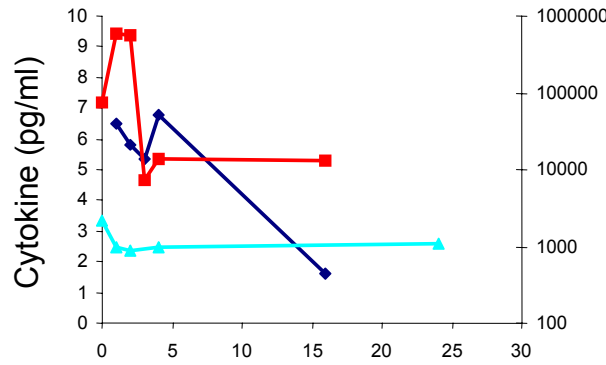
◆ Acute HIV subject ▲ HIV negative subject

Plasma

TNF α

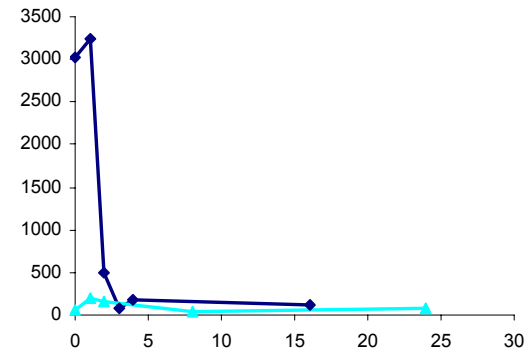
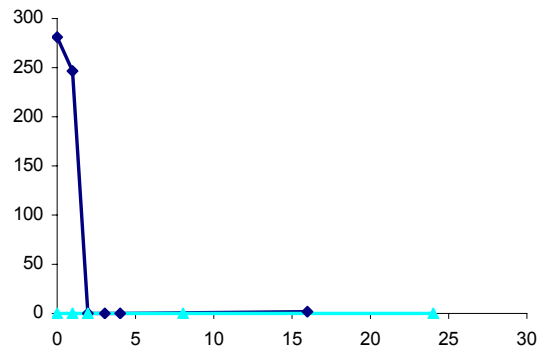
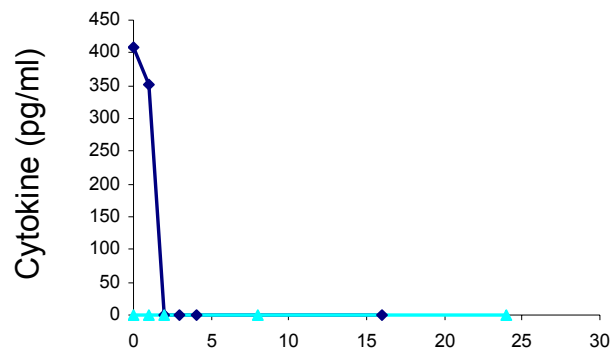
IL-1 β

IL-8



Viral load

CVL



Weeks from enrolment

Elevations in CVL cytokine/chemokine levels in AHI

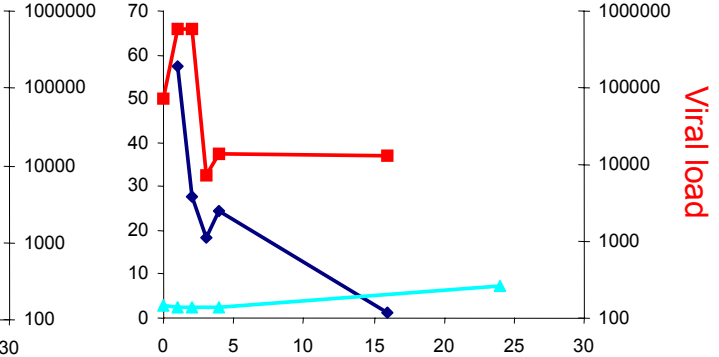
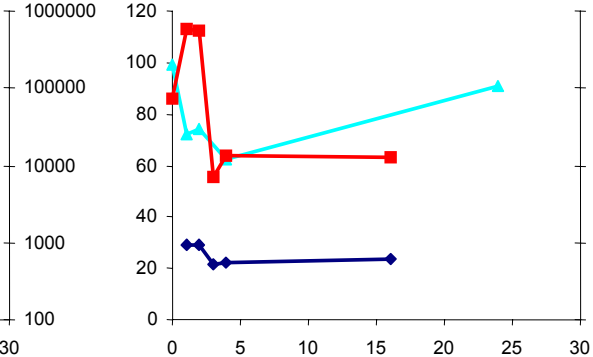
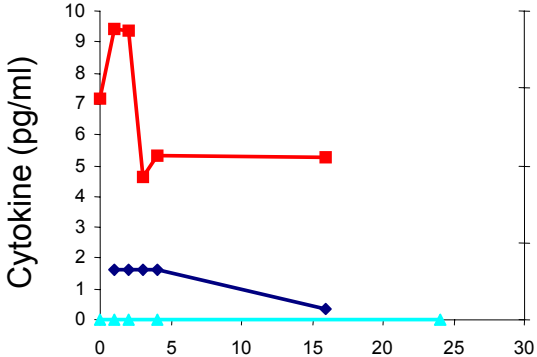
◆ Acute HIV subject ▲ HIV negative subject

Plasma

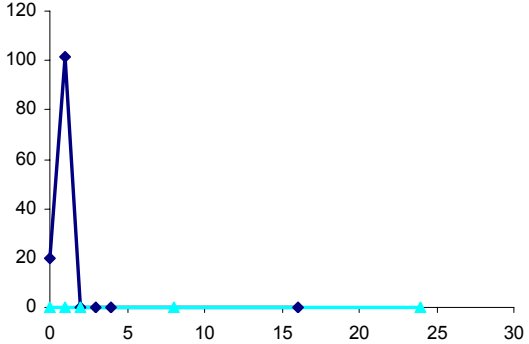
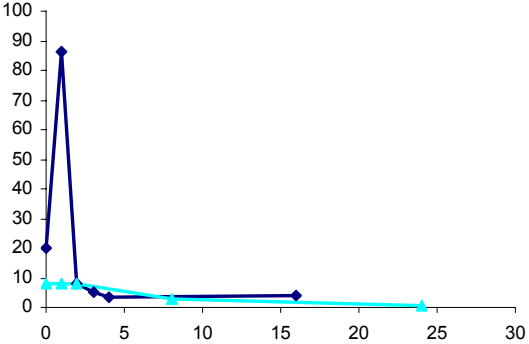
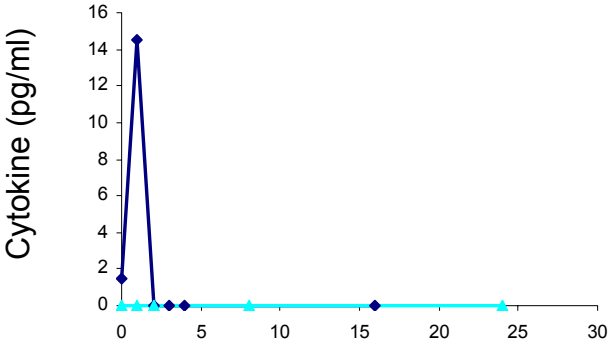
IFN γ

MIP-1 β

IL-10



CVL



Weeks from enrolment

Preliminary observations from analysis of changes in cytokine/chemokine levels in CVL during AHI

Certain analytes were highly elevated in CVL at the earliest timepoint studied suggestive of a local pro-inflammatory response prior to systemic immune activation

Other analytes were transiently elevated in CVL around the peak in plasma viraemia, perhaps reflecting delayed local induction of antiviral factors and/or production as a consequence of systemic immune activation

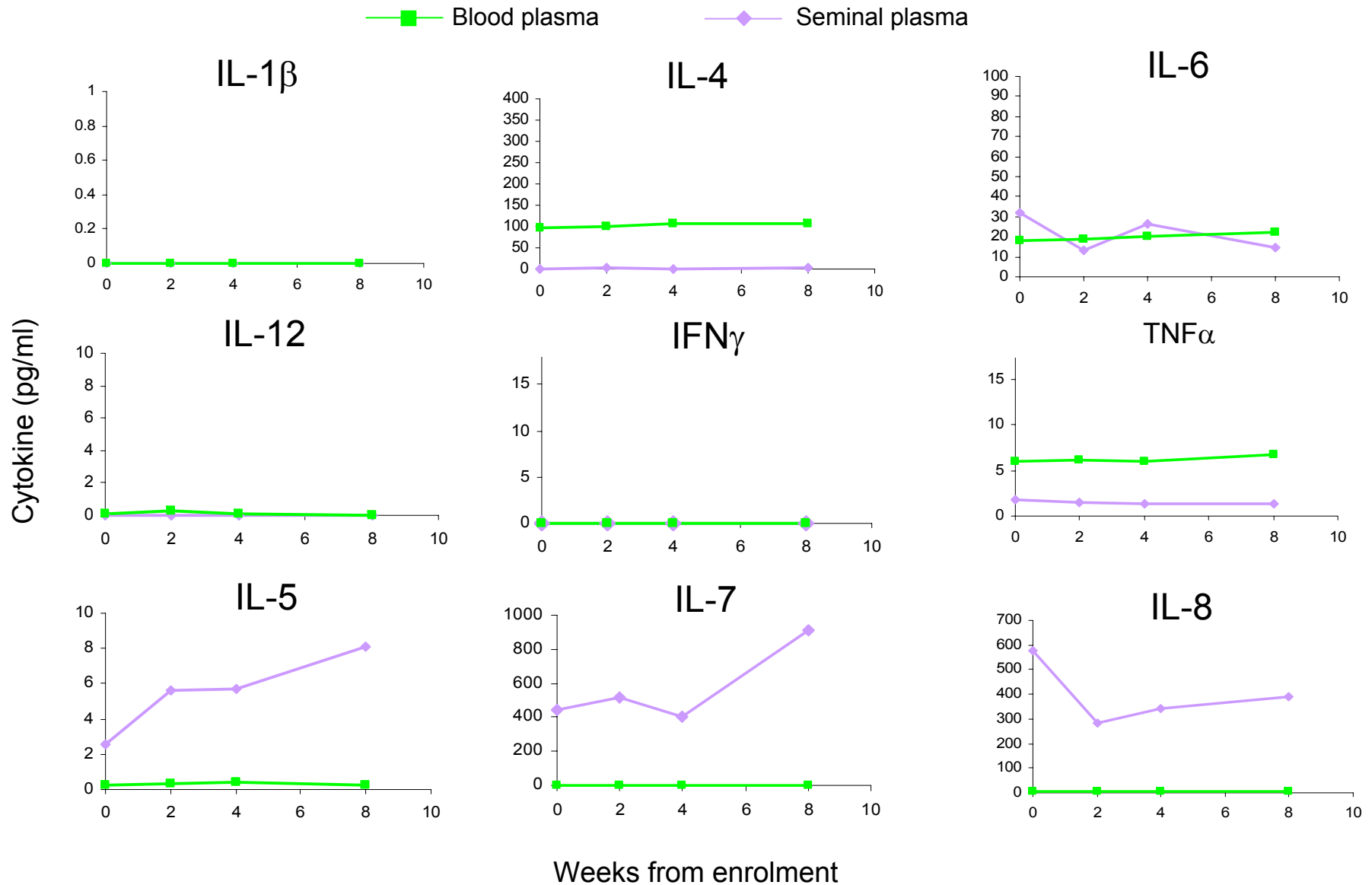
Rapid up-regulation of pro-inflammatory cytokines at mucosal infection sites may promote local viral replication and spread. Antiviral cytokines/chemokines may not be elevated rapidly enough to contain/eliminate viral replication at local sites

Analysis of cytokine/chemokine levels in mucosal fluids in AHI: Seminal Plasma

Aim: To gain insight into the nature and kinetics of innate responses in the seminal compartment and their potential impact on virus transmission during AHI

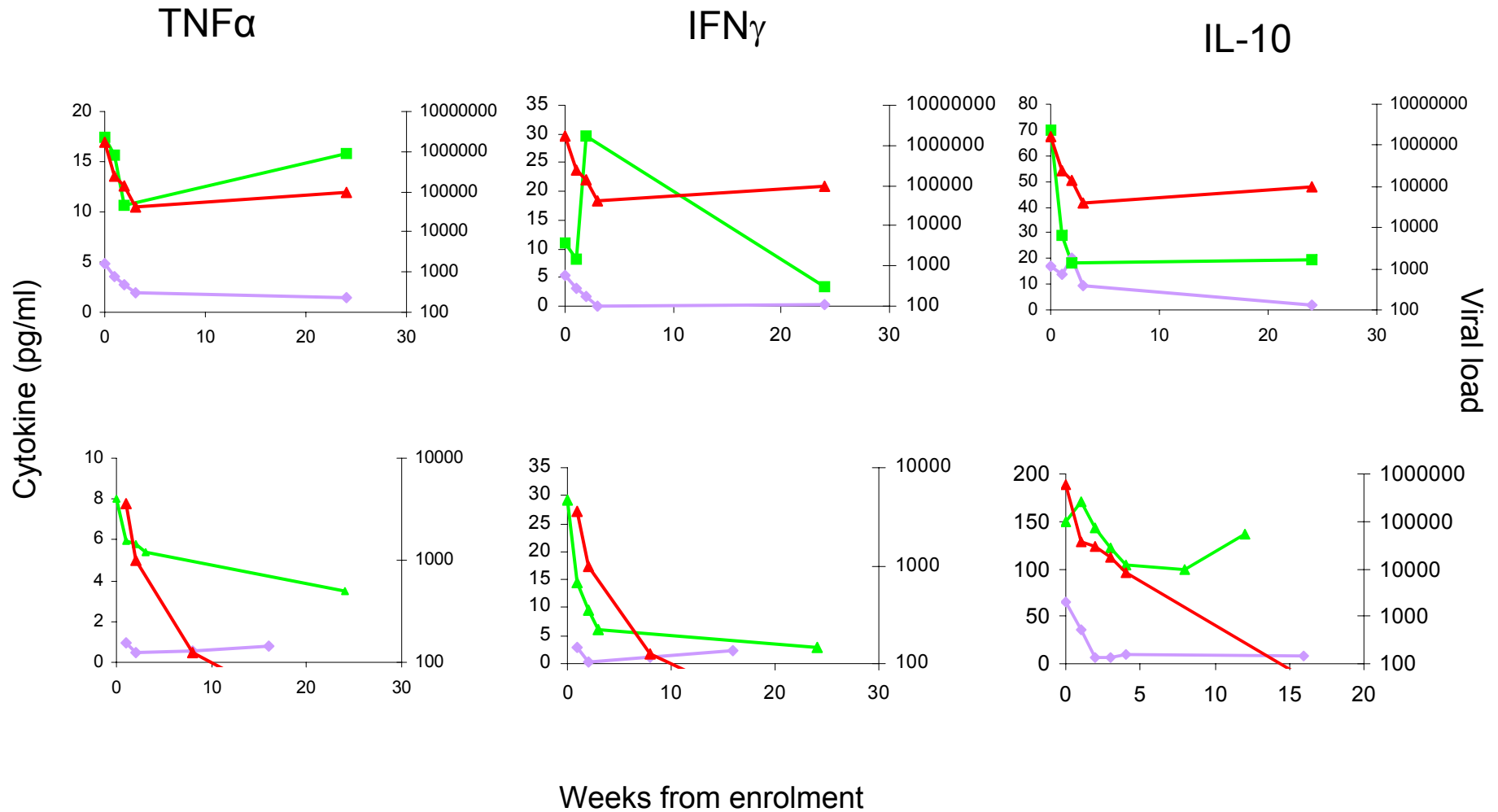
Cytokine and chemokine levels analysed in seminal plasma samples and matched blood plasma samples from male AHI subjects and HIV-negative control subjects from CHAVI 001

Cytokine/chemokine levels in seminal plasma from HIV-seronegative subjects



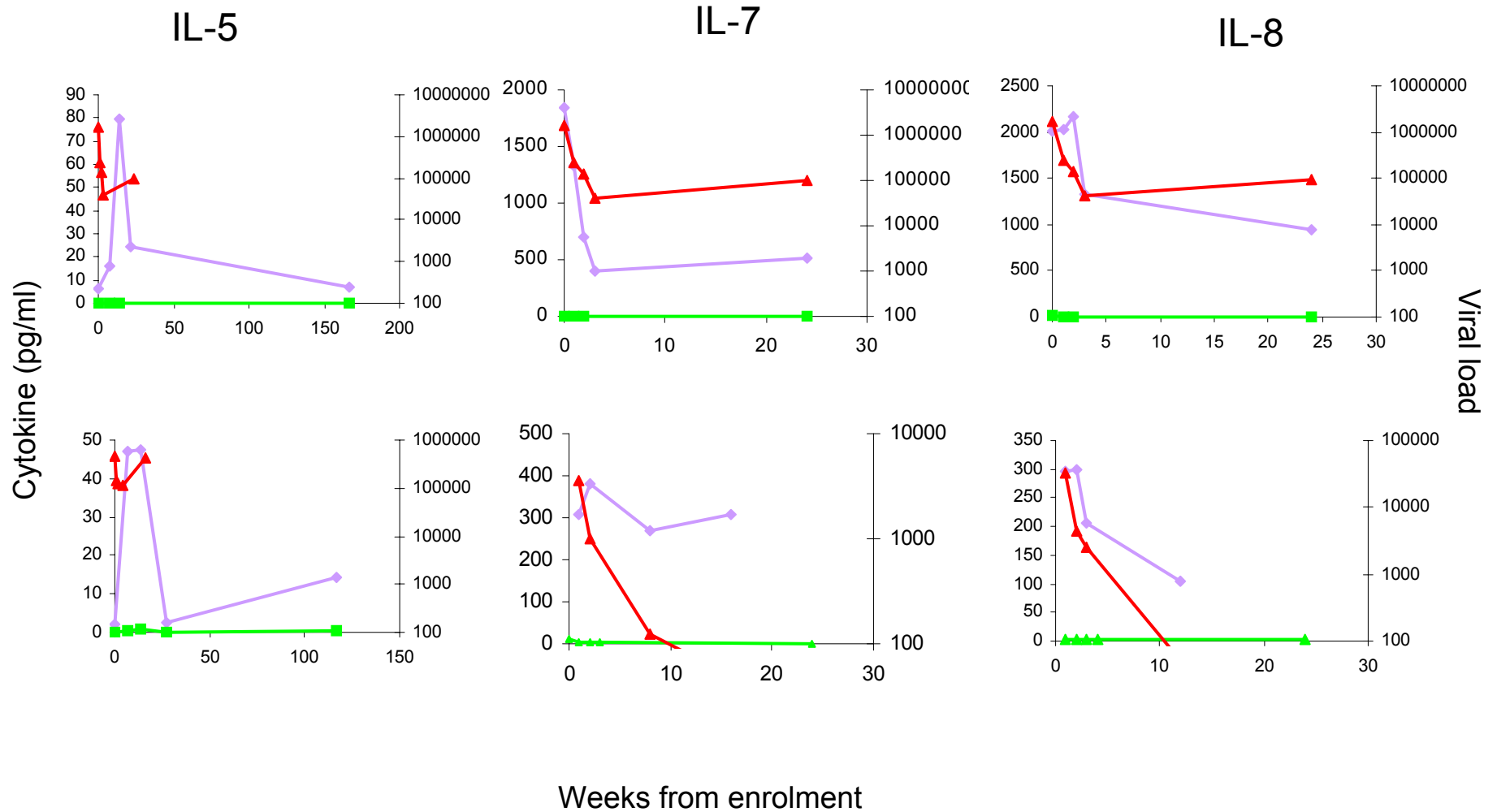
Modest elevations in seminal plasma cytokine/chemokine levels occur in AHI in parallel with systemic increases in analyte levels

▲ Plasma viral load
 ■ Blood plasma
 ◆ Seminal plasma



Analytes normally present at relatively high levels in seminal plasma are also elevated in AHI

▲ Plasma viral load
 ■ Blood plasma
 ◆ Seminal plasma



Preliminary observations from analysis of changes in cytokine/chemokine levels in seminal plasma during AHI

Modest elevations in seminal plasma cytokine/chemokine levels occur in AHI coincident with systemic increases in analyte levels

These elevation could be a result of influx from systemic responses or local production of cytokine and chemokines

Antiviral cytokines/chemokines may contribute to control of local virus replication.

Local pro-inflammatory cytokine production may lead to increased viral titres in semen and may enhance viral transmission

Future plans:

Increase the n of subjects studied to gain a clearer picture of the kinetics of cytokine/chemokine elevations in CVL and seminal plasma

Analyse relationships between cytokine/chemokine levels in CVL and seminal plasma with peak viral titre in AHI and set-point viral load established

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