HIV-1 viral load blips are of limited clinical significance

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Many patients on highly active antiretroviral therapy (HAART) who achieve undetectable HIV-1 RNA levels experience transient episodes of detectable viraemia or blips, suggesting there is incomplete suppression of viral replication. This raises concern that drug resistance mutations could develop and cause eventual treatment failure. However, data from recent studies indicate that most blips are actually random biological and statistical variations around a mean viral load below detectable levels (<50 copies/mL) or due to false elevations of viral load from laboratory processing artefacts. Blips are not typically associated with the development of resistance mutations and most importantly are not associated with virological or clinical failure of previously adequate HAART.

Keywords: HIV, genotypes, HAART, drug resistance

Introduction

The current standard treatment for patients with HIV infection is highly active antiretroviral therapy (HAART). While this therapy can significantly decrease HIV RNA levels and permit immune reconstitution, complete viral eradication remains elusive due to the existence of long-lived reservoirs such as latently infected CD4+ resting memory T-cells. Therefore, the goal of HAART is to minimize active viral replication to avoid emergence of drug resistance by maintaining plasma virus levels below the limit of detection of current ultrasensitive assays (<50 copies/mL). However, many patients on HAART with full suppression of viraemia to <50 viral copies/mL experience ‘blips’, defined as intermittent episodes of detectable low-level viraemia which return spontaneously to an undetectable range without any change in therapy1–5 (Figure 1). These occurrences are distinct from episodes of persistently detectable or episodic high-level viraemia observed in some patients. Serious concerns have been raised regarding the clinical significance of blips; specifically it is unclear whether they represent inadequate viral suppression and bursts of active viral replication with consequential development of drug resistance. Blips have generated much anxiety and uncertainty among clinicians and patients alike about the adequacy of individual HAART regimens, sometimes leading to alterations of therapy.

Blips are random variations around an undetectable mean viral load

Blips are not associated with long-term clinical failure in most studies.1–4,6,7 Havlir et al.1 conducted the first detailed examination of blip data from two clinical trials in which patients received indinavir (a protease inhibitor) and two nucleoside analogue RT inhibitors. In this study, blips were associated with higher steady-state levels of viraemia but were not associated with virological failure for up to 4.5 years (P = 0.53). Similarly, there was no correlation between blips and subsequent clinical failure in two studies of patients taking NNRTI-based HAART.6,7 Nettles et al.8 recently published data from a prospective analysis of blips using frequent viral load sampling (every 2–3 days) for 3–4 months in a group of 10 HIV-infected individuals. This study

Figure 1. Blips are defined as intermittent episodes of detectable low-level HIV-1 viraemia >50 copies/mL which are preceded and followed by viraemia in the undetectable range without any change in therapy. Episodes of persistently detectable or high-level viraemia are not considered blips.

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revealed that blips represent random variations around a mean viral load level <50 copies/mL. Plasma viral loads were measured in two independent laboratories using the same ultrasensitive assay. Blips were detected in 9 of 10 patients and of the 713 total viral load measurements, 26 (3.6%) were >50 copies/mL, constituting 18 total blips. Nine of these were detected solely by one laboratory, eight only by the other and one by both. Despite the use of the same assay with comparable sensitivities, the concordance between the two labs was poor. Moreover, the proportion of viral load measurements >50 copies/mL was consistent with random biological and statistical variations around a mean viral load level of 10–20 copies/mL. The apparent random nature of blips may explain their lack of association with increased risk for virological failure observed in prior studies.1–4,6,7

Blips are laboratory assay artefacts

Blips may also be attributed to laboratory processing artefacts as evidenced by studies of Stosor et al.9 who confirmed artefactual elevations of viral loads with the use of Plasma Preparation Tubes™ (PPT™) during collection of blood samples as compared with use of EDTA tubes. Fifty-six patients receiving HAART with ≥3 consecutive undetectable viral loads from plasma collected in EDTA tubes subsequently underwent an 8 month period of plasma collection with PPT™. Significantly more patients (69.6% versus 5.4%, P < 0.0001) experienced viremia with PPT™ use than with EDTA tubes and in 60.7% of these patients, the low-level viremia resolved when use of EDTA tubes was resumed. The manufacturers of PPT™ found similar results when comparing the two plasma collection methods and issued guidelines for proper specimen processing when using PPT™ for the collection of blood for viral loads.10 While blips generated by laboratory assay artefacts are of no direct clinical significance, they can significantly increase patient anxiety, complicate clinical decision making and confound interpretation of research data. Given this, we recommend caution when using PPT™ for the collection of blood for viral load measurement, and we urge thorough validation of new viral load assays and blood collection procedures as they become available.

Blips and development of antiretroviral drug resistance

Previous studies have reported the emergence of new drug resistance mutations in association with blips.11–13 However, these observations have been complicated by limited assessment of pre-existing mutations as well as poor sensitivity of the genotyping assay employed. Nettles et al.8 utilized an ultrasensitive genotyping method to characterize nearly 1000 viral clones obtained before, during and after blip occurrences. No new resistance mutations were identified. Importantly, viruses obtained during blips were not genetically distinct from non-blip samples suggesting no significant viral evolution during blip episodes (Figure 2). Also of note, no correlation was found between patients with greater number of pre-existing resistance mutations and frequency of blips.

Conclusions

Existing data suggest that most blips represent normal biological and statistical variations around a mean viral load <50 copies/mL.

Figure 2. Viral load and genotype over time of a theoretical HIV-infected individual. At baseline, ultrasensitive genotyping techniques identify three populations of HIV clones with a variety of mutational combinations present in the subject’s plasma. The subject had two blips, beginning around visit day #15 and #27. Viral species isolated on blip days were genotypically identical to those viral species isolated at baseline and on days following the blips. No new resistance mutations were identified during or immediately following blips.

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Transparency declarations

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References


