

Blips and its clinical relevance in HIV Patients on Treatment

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Abstract

Background: : With HAART being used extensively ,transiently detectable viremia, usually 50-400 copies/ml, has been found to be a common phenomenon, occurring in about one-quarter of HIV/AIDS patients who had achieved viral suppression below the limits of quantification while remaining on the same antiretroviral regimen. Though measurable viremia may be a harbinger of drug resistance and treatment failure ,and may simply reflect variability in the assay, such as that resulting from specimen processing, or could be caused by extraneous factors, such as immunization or intercurrent illness , usually these’’ blips of viremia ‘ appear to represent no increased risk for subsequent virologic rebound. Rebound to persistent levels of viremia of 50-400 copies/ml occurred in fewer than 5% of patients, and lasting rebound viremia > 400 copies/ml, 'virologic failure,' occurred in fewer than 10%. There was no statistically significant evidence that patients who had had a previous episode of transient viremia were at a greater risk of developing persistent viremia than those who did not experience transient viremia. The characterization of this phenomenon (low viremia) in the setting of clinical practice including patients both naive and experienced to antiretroviral drugs and on both protease inhibitor (PI)-based and non-PI-based regimens in terms of long-term virologic and immunologic outcomes, are very important in the outcome of HAART ..

Aim & Objectives To examine and disseminate- the prevalence and clinical correlates of subsequently measurable viremia from studies done on HIV-infected patients who have achieved viral suppression below the limits of quantification (< 50 copies/ml)

Methods/Study Design :

Data Source The scientific literature and eligible materials were surveyed related to the topic of ‘ Blips and its clinical correlates ‘ and was found one ‘The Centers for Disease Control and Prevention's (CDC) sponsored **HIV Outpatient Study (HOPS)**, into which patients had been continuously recruited, to date collected data on the course of disease for more than 5500 HIV-infected, non-hospitalized patients, who have been seen in about 106 000 outpatient visits since 1992.

Patients: Patients who , had atleast two consecutive HIV-1 RNA levels < 50 copies/ml (minimum, 2 months apart) that were followed by at least two more viral level determinations

while remaining on the same antiretroviral therapy (ART) between January 1997 and June 2000 (median 485 days). Transiently viremic patients were defined having a subsequently measurable viremia but again achieved suppression < 50 copies/ml.

Design : Non-randomized dynamic cohort study of ambulatory HIV patients in nine HIV clinics in eight cities and host of other Studies on 'blips'

Results/Findings : Of the 448 patients, 122 (27.2%) had transient viremia, 19 (4.2%) had lasting low-level viremia and 33 (7.4%) had lasting high-level viremia (defined as 50-400 and > 400 copies/ml, respectively). Only 16 (13.1%) of those who had transient viremia later had persistent viremia > 50 copies/ml. The occurrence of transient viremia did not vary with whether the patient was ART-naive or experienced ($P = 0.31$), or currently taking protease inhibitors or not ($P = 0.08$). On consistent ART, the median percentage increase in CD4 cell count was statistically different between subgroups of the cohort (Kruskal-Wallis, $P = 0.002$).

Study Limitations (optional): The definition of a "viral blip" or transiently detected low-level viremia is evolving, but a number of working definitions have been used for research purposes. As a result, care must be taken when comparing data regarding the significance and management of blips

Conclusion : Transiently detectable viremia, usually 50-400 copies/ml, was frequent among patients who had two consecutive HIV-1 RNA levels below the limits of quantification. In this analysis, such viremia did not appear to affect the risk of developing lasting viremia. Caution is warranted before considering a regimen as 'failing' and changing medications.

Keywords: HAART (Highly Active Anti retro viral therapy) Blips, HOPS (The HIV Outpatient Study) virologic failure, naive and experienced patients, regimens containing PIs (Protease Inhibitors),

Background

With the introduction of potent antiretroviral therapy ,the morbidity and mortality associated with HIV-1 infection has declined sharply. Patients adherent to suppressive regimens are able to achieve plasma HIV-1 RNA levels below the limit of quantification by established assays. Occasionally, transient low-level viremia (ie, a viral blip) is detected by viral load assays, often causing anxiety on the part of patients and clinicians about pending virologic failure or the emergence of drug resistance. The occurrence of viral blips may lead clinicians to order costly and unnecessary tests and alter medication regimens of otherwise well-controlled patients.

An increased frequency of viral blips has been reported with the newer-generation viral load assays that are now in widespread use. Increased reporting and awareness of viral blips has led to recent advances in the understanding of the etiology and significance of transient low-level viremia. However, the existing data regarding the associations between viral blips and clinical factors such as medication adherence, emergence of resistance mutations, and subsequent

virologic failure, are sparse and sometimes conflicting.] Few prospective study results are available and inconsistencies in study design and viral blip definitions often make cross-study comparisons and extrapolation to clinical management difficult. For these reasons, it is important for HIV clinicians to understand the content and quality of the data surrounding viral blips and how differences in viral load testing strategies may lead to variations in blip frequency.

With the introduction of more sensitive laboratory methods to quantify plasma HIV-1 RNA levels, an increase in the number of episodes of intermittent low-level viremia (ie, viral blips) has occurred among patients on stable antiretroviral regimens with previously undetectable viral loads. The occurrence of viral blips may lead clinicians to order costly and unnecessary tests and alter medication regimens for otherwise well-controlled patients. It is important for HIV clinicians to understand the content and quality of the data on viral blips and how differences in viral load testing strategies may lead to variations in blip frequency.

Several studies have suggested that achieving plasma HIV-1 RNA levels below the limits of detection (as low as < 20 copies/ml) within several weeks of initiating a new regimen is predictive of long-term success of highly active antiretroviral therapy (HAART). However, many HIV-infected patients who achieve viral suppression below the limits of quantification while on HAART have measurable, but transient, viremia subsequently. It is still unclear, however, whether such transiently detectable viremia is detrimental to longer-term virologic control. On one hand, measurable viremia may be a harbinger of drug resistance and treatment failure. It has been suggested that low-levels of viremia may alter viral dynamics and change the slope of the decay curve of latently infected cells. On the other hand, transiently measurable viremia may simply reflect variability in the assay, such as that resulting from specimen processing, or could be caused by extraneous factors, such as immunization or intercurrent illness. This study further characterizes this phenomenon in the setting of clinical practice including patients both naive and experienced to antiretroviral drugs and on both protease inhibitor (PI)-based and non-PI-based regimens in terms of long-term virologic and immunologic outcomes.

Viral ‘blip’ definitions

The definition of a “viral blip” or transiently detected low-level viremia is evolving, but a number of working definitions have been used for research purposes. As a result, care must be taken when comparing data regarding the significance and management of blips.

The most common definitions describe blips as isolated viral load measurements above the assay detection limit (usually 50 HIV-1 RNA copies/mL) but less than 500 copies/mL to 1000 copies/mL, in patients with previously undetectable HIV-1 RNA and in whom the subsequent test is again below the limit of quantification. Many criteria require that patients are stable on a specific antiviral regimen before and after blips. Another definition describes a blip as a detectable HIV-1 RNA level (above 40 or 50 copies/mL but no more than 1000 copies/mL) occurring between 2 negative assays no more than 2 months apart.] Some experts have proposed the use of even lower viral load cutoffs such as 200 copies/mL, but this more stringent definition has not been widely adopted. Most definitions stress that the blips must be succeeded by a return to an undetectable virus load on the same antiviral treatment,] but the timing of the subsequent negative result is highly variable among studies.

As a result of the growing number of viral blip studies and data surrounding these transient events, the **2009 DHHS guidelines and similarly, the 2008 IAS–USA guidelines**, define an incomplete virologic response as **“two consecutive plasma HIV RNA > 400 copies/mL after**

24 weeks or above the limit of assay detection by 48 weeks on an antiretroviral regimen.” Virologic rebound is defined as repeated detection of HIV-1 RNA above the assay limit of quantification (eg, > 50 copies/mL) after virologic suppression.’’.

Blips should not be confused with **persistent low-level viremia**, which is usually defined as detection of low levels of HIV-1 RNA in several consecutive samples. Although there may be some **overlap between the definitions of blips and persistent low-level viremia**, the clinical significance of these events is quite different, as patients with low-level viremia experience higher rates of virologic failure and immune activation whereas those with blips do not.

So Blips’ can be defined as a transient VLs (viral load) >50 c/ml, preceded and followed by measurements < 50 c/ml without a change in treatment. They are fairly common, low level (79 c/ml), transient (isolated events), unrelated to clinical events, (illness, vaccination etc), inconsistent (noted in only one of duplicate samples and appeared to represent a statistical variation around the mean VL, < 50 c/ml, suggesting most that are unconfirmed with repeat testing are errors

Etiology of Viral Blips

The cause of viral blips is likely multi-factorial and several contributing factors have been proposed to explain detection of intermittent low-level viral loads:

- **Detection of persistent or intermittent low-level releases of virus from existing reservoirs**
- **Random laboratory variation**
- **Laboratory test and operator error**
- **Decreased antiretroviral adherence**

The exact causes of transient or persistent low-level viremia are still under investigation and a detailed discussion of persistent viremia is beyond the scope of this activity. However, it is known that HIV persists in populations for long periods via resting, latently infected CD4+ T cells and macrophages. [T-cell turnover is generally very low, but virus is released quickly after cessation of suppressive therapy. [Despite fully active antiretroviral therapy, low-level viremia has been detected using ultra-sensitive and single copy assays in patients receiving suppressive therapy; this viremia is stable for least 7 years. Low-level viremia has also been detected in untreated long-term survivors of HIV infection who have minimal disease progression and undetectable viral loads.

Transient low-level viremia may represent episodes of viral replication, with cycles of infection, reverse transcription, integration, and production and release of new virus; alternatively, it may represent virus released from long-lived infected cells that is not propagated by further cycles of infection. Regardless of the cause, low levels of viremia in patients who are well controlled on otherwise suppressive antiretroviral therapy provide a rationale for the intermittent detection of blips with sensitive assays.

Several retrospective and prospective studies have demonstrated that blips are common, with the percentage of patients who experience a blip over time ranging from 10% to 40%. However, the incidence of blips from these studies is a function of the timing of patient follow-up, frequency of viral load measurements, type of assay used, and the study’s definition of viral blips. It is therefore difficult to compare the proportion of patients experiencing blips across different studies. **Table 4** summarizes results from studies that examined blip frequencies and amplitudes; blip definitions used in each study are also provided.

Methods

The scientific literature and eligible materials were surveyed related to the topic of ‘Blips and its clinical correlates’ and was found one --‘The Centers for Disease Control and Prevention's (CDC) sponsored **HIV Outpatient Study (HOPS)**, into which patients had been continuously recruited, to date collected data on the course of disease for more than 5500 HIV-infected, non-hospitalized patients, who have been seen in about 106 000 outpatient visits since 1992.

A detailed description on ‘HOPS’ is written below.

The HIV Outpatient Study (HOPS)

The Centers for Disease Control and Prevention's (CDC) ongoing HIV Outpatient Study, into which patients are continuously recruited, has to date collected data on the course of disease for more than 5500 HIV-infected, non-hospitalized patients, who have been seen in about 106 000 outpatient visits since 1992.^[4] The present analysis includes data on patients seen from 1 January 1997 to 30 June 2000. The study sites are nine clinics (seven private and two public) in eight United States cities (Chicago, Illinois; Denver, Colorado; Oakland and San Leandro, California; Philadelphia, Pennsylvania; Stony Brook, New York; Tampa, Florida; Washington, DC) that provide care for at least 150 HIV-infected patients each per year. HOPS participating physicians routinely care for hundreds of HIV-infected patients and have extensive experience treating HIV. This study has been reviewed and approved by CDC and local institutional review boards since its inception.

Information in five general categories is abstracted from the chart for each outpatient visit and entered electronically by trained research coordinators. The data are compiled centrally, reviewed, and routinely processed for quality control. Because the participating physicians are the source of primary care for these patients, all symptoms, diagnoses, and treatments since the previous visit, including interim changes, are noted at each clinic visit. The categories of information abstracted are as follows: demographic characteristics and risk factors for HIV infection; symptoms; diagnosed diseases (both definitive and presumptive diagnoses); medications prescribed, including the dose and duration; and laboratory values, including CD4 cell counts and measurements of plasma HIV-1 RNA.

Patients

During the period of present analysis, there were 3772 active patients in the HOPS database, 448 of whom met the inclusion criteria for this analysis. To be included, patients must have had two consecutive HIV-1 RNA levels below the limits of detection (< 50 copies/ml), 2 or more months apart, and at least two subsequent viral load measurements with no change in antiretroviral therapy (ART). Dose modification of an antiretroviral agent was not considered a change in therapy, nor was a treatment interruption of less than 30 days. In this select cohort from the HOPS, no patient had a recorded complete interruption in ART. A patient was not included if the only detectable viral load was the last one he or she had during the study period. Measurements of HIV-1 RNA were performed using the reverse transcriptase polymerase chain reaction RT-PCR technique (Amplicor HIV-1 Monitor, Roche Diagnostics Corporation, Indianapolis, Indiana, USA) in 91.1% of the assays and by the b-DNA technique (Chiron Corporation, Emeryville, California, USA) in the remainder.

For the purpose of analysis, patients were classified into one of four groups. The first group were 'suppressed' patients - that is, patients who maintained HIV-1 RNA levels below the limits of quantification on all determinations throughout the study period.

The second group, 'transiently viremic' patients, were those who had measurable viremia ('blips') after two determinations < 50 copies/ml and who again achieved suppression below the limits of quantification. This group were examined to see whether, during the remainder of the period of observation, there was a subsequent episode of transient or lasting detectable viremia after the first blip and return below the limits of quantification.

The third and fourth groups of analysis were patients with persistent viremia, i.e., 'lasting rebound' viremia after two determinations < 50 copies/ml; these patients never again achieved viral suppression below the limits of quantification during the study period. Because persistent viremia may be clinically important, these patients were further grouped as 'high level', if the level of measurable viremia was ever > 400 copies/ml, and 'low-level' if measurable viremia was persistently at levels of 50-400 copies/ml. These numerical cut-off points were chosen based on the limits of detection of the widely available viral load assays.

Statistical Analysis

Data were analyzed with SAS software (version 6.12; SAS Institute, Cary, North Carolina, USA). Patient characteristics, prevalence, and clinical correlates of measurable viremia were compared across groups, classified by level of virologic control, using chi-square analyses for categorical variables and the non-parametric Kruskal-Wallis test of multiple medians for continuous variables. All medians are reported with interquartile ranges (IQR) Q1-Q3 in the tables. Comparisons of risk between subgroups of the cohort for subsequent viremia after the initial HIV-1 RNA measurements below the limits of detection were made with risk ratios.

Results

Patient Characteristics

The analyses include data collected during the period 1 January 1997 to 30 June 2000 on 448 HIV-infected persons who met study inclusion criteria. Patients were classified according to their level of virologic control. Except for payer status, no statistically significant differences were found between groups compared with regard to a number of demographic and clinical variables examined, including age, sex, race, primary risk behavior, highest level of education, baseline CD4 cell count and HIV-1 RNA level ([Table 1](#)).

Given the dynamic nature of this cohort, the study period differed for each patient. The median length of observation was 485 days (69 weeks), which did not differ statistically among the groups. However, the number of follow-up viral load measurements after achieving viral suppression below the limits of quantification did differ among compared groups (Kruskal-Wallis test, $P = 0.0002$) ([Table 1](#)).

Prevalence and Clinical Correlates of Transient and Lasting Viremia

Of all 448 patients, 274 (61.2%) maintained viral loads below the limits of quantification throughout the study. The only association with maintenance of undetectable viral loads was health payer status: 232 (64.6%) of 359 privately insured patients, but only 30 (47.6%) of 63 patients with public subsidy (Medicare, Medicaid), maintained viral levels < 50 copies/ml

throughout the study period [relative risk (RR), 1.36; 95% confidence interval (CI), 1.04-1.78; **Table 1**).

Transient viremia occurred in 122 (27.2%) of the study participants and nine (7.4%) of them had more than one blip (i.e., 22.5 blips/100 person-years). Seventy-eight percent of the time, these episodes were of low-level viremia, 50-400 copies/ml. After the first detectable measurement, 106 (87%) of patients returned below the limits of quantification on the next measurement; all transiently viremic patients returned below the limits of quantification by the third measurement after the blip. On continued follow-up, however, 16 (13.1%) of the original 122 patients experiencing transient viremia subsequently had a 'rebound' with viremia > 50 copies/ml that never returned below the limits of quantification during the study period. Of these 16 patients, the previous episode of transient viremia was low-level in 75%; none was a patient who had experienced more than one blip episode.

Nineteen (4.2%) of the 448 patients in the study population had a rise from 'undetectable' viral loads to lasting levels of 50-400 copies/ml (low-level rebound), and 33 (7.4%) had lasting viremia > 400 copies/ml (high-level rebound). During the period of study, 16 (13.1%) of the 122 patients who had transient viremia developed persistent low or high level ('rebound') viremia at some later point, compared with 52 (16.0%) of the remaining 326 patients in the cohort, but the difference was not statistically significant (RR, 0.82; 95% CI, 0.49-1.38). The median first detectable RNA level was 96 copies/ml among transiently viremic patients, 94 copies/ml among the lasting low-level viremic patients and 426 copies/ml among the lasting high-level viremic patients (Kruskal-Wallis test, $P = 0.0001$). Median CD4 cell counts at the time of first detectable

RNA were 486.5 10^6 cells/l among transiently viremic patients, 628 10^6 cells/l among

the patients with lasting low-level viremia, and 550 10^6 cells/l among the patients with lasting high-level viremia. There was no significant difference between the groups for this parameter (Kruskal-Wallis test, $P = 0.25$).

Two important clinical parameters, antiretroviral experience and composition of the antiretroviral regimen (PI-containing or non-PI-containing) were compared for their association with transient viremia. There was no evidence to suggest that blips were more likely to occur among patients who were previously taking or not taking ART (ART-naive versus ART-experienced patients; $P = 0.31$), or in patients on PI regimens versus those on non-PI regimens ($P = 0.08$). However, patients with persistent rebound viremia had been exposed to a greater number of antiretroviral agents than those who remained suppressed or who experienced a transient episode of viremia (Kruskal-Wallis test, $P = 0.01$). (**Table 2**).

CD4 Cell Count Response to Consistent Antiretroviral Therapy

As an index of immune reconstitution, CD4 cell counts were compared from before the start of the antiretroviral regimen to the last recorded measurement at the end of the study period. Recall (**Table 1**), the median length of follow-up did not significantly differ among the groups. Interestingly, on consistent ART, the median percentage increase in CD4 cell count was statistically different between subgroups (Kruskal-Wallis test, $P = 0.002$; **Table 3**

Discussion

Several retrospective and prospective studies have demonstrated that blips are common, with the percentage of patients who experience a blip over time ranging from 10% to 40%. However, the incidence of blips from these studies is a function of the timing of patient follow-up, frequency of viral load measurements, type of assay used, and the study's definition of viral blips. It is therefore difficult to compare the proportion of patients experiencing blips across different studies. Table 1 summarizes results from studies that examined blip frequencies and amplitudes; blip definitions used in each study are also provided

Another retrospective study : of 2720 patients showed that 28.6% experienced blips within a mean time of 22 months, and that the number of blips was not associated with age, sex, risk group, treatment modality, or time from HIV diagnosis. In a prospective study of 10 patients receiving suppressive antiretroviral therapy, viral load monitoring every 3 days detected blips in 9 out of 10 patients; these results suggest that if tested frequently enough, blips will be detected in most patients.

In the above prospective study, blip frequency was not associated with sex, race, age, CD4+ cell count nadir, CD4+ cell count at entry, pretreatment viral load, duration of infection, duration of virologic suppression, or intercurrent illnesses. Similarly, the only predictors of intermittent viremia in an earlier retrospective investigation of a large clinical trial were baseline HIV-1 RNA level and being randomized to single or dual antiretroviral maintenance therapy. Alternately, in a post-hoc analysis from studies of lopinavir/ritonavir in combination with nRTI backbones, baseline viral load or CD4+ cell count were not associated with blips. Median viral load amplitudes from all viral blip studies were low and ranged from 76 copies/mL to 350 copies/mL, although median values were less than 200 copies/mL in a majority of studies, as listed in **Table 4**.

There is now growing evidence that viral blips in the setting of otherwise suppressive therapy occur at random and represent intermittent detection of viremia around the assay limit of quantification. The lower limits of detection for many testing platforms are not necessarily fixed barriers, and there can be random variation of detection around the lower-level viral load cutoffs. For example, investigators from the above prospective study of 10 patients concluded that blips represent random variation around a mean viral load level of about 50 copies/mL. In another study of 123 HIV-infected patients initiating antiretroviral therapy over a mean period of 2.6 years with a mean of 26 viral load measurements per patient demonstrated a frequency of 0.09 +/- 0.11 blips per test. These results suggest that blip frequency was random and those that occurred less than 3 weeks apart were likely to be part of the same episode of transient viremia. Further analysis of these data provided evidence that blips could not be explained purely from assay errors.

A similar study of 272 patients on successful antiretroviral therapy demonstrated that blips may be the result of random sampling and detection of asynchronous and overlapping viremic episodes

Transiently detectable viremia, usually 50-400 copies/ml, was found to be a common phenomenon, occurring in about one-quarter of patients who had achieved viral suppression below the limits of quantification while remaining on the same antiretroviral regimen. These blips of viremia appear to represent no increased risk for subsequent virologic rebound. Rebound

to persistent levels of viremia of 50-400 copies/ml occurred in fewer than 5% of patients, and lasting rebound viremia > 400 copies/ml, 'virologic failure,' occurred in fewer than 10%. There was no statistically significant evidence that patients who had had a previous episode of transient viremia were at a greater risk of developing persistent viremia than those who did not experience transient viremia.

The phenomenon of transient viremia has been previously examined in a small case series,^[5] in the setting of clinical trials, and in two retrospective cohort studies.¹ While comparison between studies is problematic as study definitions are not consistent, investigators in one clinical trial (ACTG 343) found that intermittent viremia of 50-200 copies/ml occurred in 40% of patients, while intermittent viremia to levels > 200 copies/ml occurred in 20% of patients. They also concluded that intermittent viremia was not associated with a greater risk of viral rebound. Data on low-level viral rebound and blips of 50-500 copies/ml has also been reported from the Swiss HIV Cohort Study and the Frankfurt HIV Clinical Cohort (seen in 32.5% of patients, which is 37.4 episodes/100 person-years) Thus, overall prevalence of this phenomenon appears similar across all studied populations.

In the present study, our data suggest that CD4 cell count response to ART, but not antiretroviral experience (as opposed to no prior ART treatment) or PI use, was correlated with transient viremia. The immune response (CD4 cell rise) among the transiently viremic patients seen in this study contrasts somewhat with other reports. For example, investigators from three London HIV centers have suggested that CD4 cell count response to therapy was not as large in those experiencing virological blips as in those maintaining undetectable viral loads. Similar findings were demonstrated in a study from the Johns Hopkins cohort, with those having a sustained virologic response to HAART experiencing the greatest rise in CD4 cell count at 24 weeks of study.

A rise from an 'undetectable' RNA level on any given measurement is not necessarily an indication of failure of an antiretroviral regimen. The great majority of patients will again have 'undetectable' viral loads without any change in ART. Although patients with lasting rebound may have higher viral loads at first detection, there is no way to predict at this point which patients will subsequently return to undetectable levels. In the present study, all those whose viremia was transient returned below the limits of detection by the third follow-up measurement. Therefore, only a small proportion of patients (7.4%) had lasting viremia > 400 copies/ml, requiring adjustments in their antiretroviral regimen.

The patients and physicians participating in the HOPS were diverse and reasonably representative of the HIV-infected population receiving medical care in the United States. Since the HOPS database is a dynamic cohort, patients are followed for various times; additional data points could result in patients being reclassified to another group. Interestingly, however, the longest median length of follow-up was among those patients who experienced transient viremia. As would be expected from a clinical perspective, viral load measurements were obtained more often in those patients who experienced transient viremia and lasting viremia > 400 copies/ml. It is possible that blips were discovered because of more frequent sampling in those groups. However, when the length and frequency of follow-up were compared among the transiently viremic patients and the patients with low- and high-level lasting viremia, from the time of first detectable viremia, there were no differences between the groups. It is important to note that baseline CD4 cell counts and HIV-1 RNA levels were comparable among the groups. The power

of the study to detect differences between groups was limited by the small number of patients with lasting, low-level and high-level viremia.

With the newly revised US Department of Health and Human Services guidelines issued in February 2001, the 'when to start' question has been revisited. There are fewer data on the 'when to switch' question, i.e. what defines a failing regimen. Clinically, there appears to be a difference between having ever achieved viral suppression below the limits of quantification and remaining below this threshold after initial suppression. This is particularly relevant given the current limited therapeutic options available to many patients and the mounting evidence of toxicities of some of these agents. Caution is warranted before considering a regimen 'failing' and changing therapies. This clinically oriented observational study does not attempt to explain the etiology of this phenomenon, which is likely related to factors such as adherence or pharmacologic variables, such as achievable drug levels. Alternatively, these blips may represent truly intermittent viremia of unknown cause. Clearly, longer follow-up of patients is necessary to address such issues. The likely reality is that low levels of ongoing viral replication are constantly occurring below the limits of detection of commercially available assays; the defined thresholds are arbitrary. However, the occurrence of detectable blips should trigger the clinician to readdress the issue of adherence with the patient.

Viral blips and virologic outcome

Overall, low-level viral blips are not predictive of future adverse clinical outcomes. **Table 2** summarizes several studies that examined the association of blips and subsequent virologic failure. One early study, which defined virologic failure as any viral load below 500 HIV-1 RNA copies/mL, did show a correlation between blips and a 2-fold increase in subsequent virologic failure, but this finding has not been reproduced. A large retrospective study examined outcomes of 2720 patients who experienced viral blips. Blips were defined as a detectable viral load between 51 copies/mL and 500 copies/mL after at least 2 consecutive undetectable plasma viral load measurements during the prior 6 months. At least 1 episode of low-level viremia occurred in 28.6% percent of patients, 80.5% of whom remained on the same antiretroviral regimen after the initial blip. Of the patients who experienced blips without changing antiretroviral therapy, 9.1% developed virologic failure, defined as a further episode of low-level viremia after the initial blip. No association was found between specific antiretroviral regimens and either the frequency of blips or the occurrence of virologic failure. In a multivariate analysis that included age, sex, HIV risk behavior, CD4+ cell count, time from HIV diagnosis, treatment modality, and viral load at time of blip, only the level of viremia at the time of the blip predicted subsequent virologic failure. Results from the prospective study of 10 patients suggest that 96.4% of blips that are below 200 copies/mL are due to random variation around the limit of quantification of current HIV-1 RNA assays. If this is the case, blip amplitudes above 200 copies/mL may have greater impact on clinical outcomes. In contrast, several other studies did not show an association between blip amplitude and subsequent failure.

Other studies demonstrated similar low rates of virologic failure among patients who experience blips (**Table 5**), but in several of these studies, patients without blips had similar or slightly higher rates of virologic failure than patients with blips (**Table 5**). These observations suggest that a conservative approach can be taken in regard to the clinical management of blips. Given the modest reported association between blip amplitude and subsequent failure, further research regarding this subject is needed.

Viral blips, Antiretroviral Regimens, and Resistance Mutations

Data exploring the association between blips and the development of resistance are sparse. Some studies suggest an increased risk of resistance to reverse transcriptase (RT) and protease inhibitors (PIs) in patients who experienced blips, but these studies are limited by small sample size and the inability to differentiate between emergence of new mutations and the presence of resistance mutations that existed prior to initiation of antiretroviral therapy. Other studies, one of which incorporated frequent viral load monitoring and aggressive sampling from plasma and cellular reservoirs at baseline and prior to blips, have not shown an association between resistance and viral blips. The nature of specific medication regimens and the frequency of viral blips are controversial, but some studies suggest that NNRTI and PI usage is not associated with blip frequency or subsequent failure in these patients.

More robust data suggest that resistance is not associated with viral blips. In the prospective study of 10 patients using frequent viral load monitoring, protease and RT regions of plasma viral RNA were successfully amplified and sequenced before, during, and after blips in 9 of the 10 patients; numerous clones were also obtained from each timepoint. [New drug-resistance mutations were not detected during viral blips, and samples had genotypes that were either wild-type, or were mutations at the time of baseline sampling from plasma and cellular reservoirs prior to blips. The lack of change in virus genotype suggests that no substantial viral evolution occurred during these episodes

Although there have been a few small studies showing that resistance mutations can be detected during times of transient low-level viremia, there is growing evidence that patients who experience blips do not have a higher incidence of virologic failure requiring changes in medication regimens. This is not necessarily the case with persistent low-level viremia

Studies have demonstrated that patients who experience viral blips do not have an increased risk of virologic failure. Many of the studies that examine outcomes in these patients have follow-up times lasting longer than 1 year.

Take Home Messages

HIV-1 blips are relatively common, but the clinical significance of transient low-level viremic events is limited.

- Definitions vary as to what constitutes a viral blip. The most common definitions describe a blip as an episode of detectable viremia that falls between the lower limit of assay detection and 500 copies/mL or 1000 copies/mL and is preceded and followed by levels below the assay limit of quantification.
- Viral blips likely represent underlying transient or persistent low-level viremia that is intermittently detectable by ultrasensitive assays to quantify HIV-1 RNA.
- Viral blips are common. Studies demonstrate 10% to 50% of patients experience at least 1 blip over a period of 1 or more years. However, the incidence of blips varies depending on the frequency of viral load testing and the viral load quantification assay used.
- The incidence of blips is not related to specific antiretroviral regimens.
- Lower-amplitude HIV-1 blips are not associated with increased rates of subsequent virologic failure or the development of clinically significant drug resistance.
- Adherence is only modestly associated with viral blips, with the most robust data suggesting that decreased adherence within 1 week of the blip may be associated with a

transient low-level viremic event. Other studies have shown that antiretroviral drug levels are adequate during times of viral blips.

- Transient viremia intermittently detected by ultrasensitive assays may last up to 3 weeks, so results of viral load tests repeated too soon after the first positive result may still be positive, depending on the assay variance near the lower limit of quantification.
 - Main causes of blips are : Detection of persistent or intermittent low-level releases of virus from existing reservoirs, Random laboratory variation, Laboratory test and operator error & Decreased antiretroviral adherence
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Table 1:

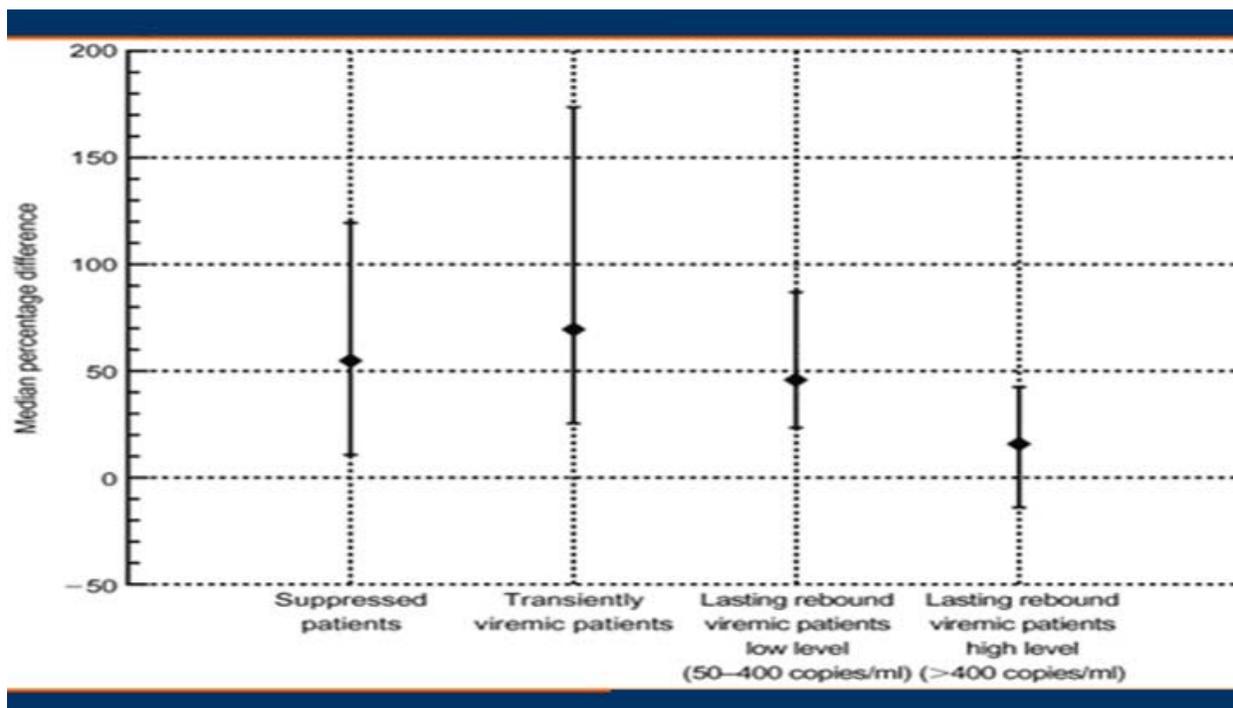


Table 2:

	Suppressed	Transiently viremic	Lasting rebound to low level ^a	Lasting rebound to high level ^b	P value ^c
Total number	274	122	19	33	
Antiretroviral experience [No. (%)]					
Naive	56 (20.4)	19 (15.6)	1 (5.3)	6 (18.2)	
Experienced	218 (79.6)	103 (84.4)	18 (94.7)	27 (81.8)	0.31
Number of antiretroviral drugs previously used [median (IQR)]	4 (3-5)	4 (3-5)	6 (4-7)	5 (3-6)	0.01
Antiretroviral regimen [No. (%)]					
Non-protease inhibitor	54 (19.7)	26 (21.3)	4 (21.0)	13 (39.4)	
Protease inhibitor	220 (80.3)	96 (78.7)	15 (79.0)	20 (60.6)	0.08

IQR, interquartile range (Q1-Q3).

^aLow level, to 50-400 copies/ml.

^bHigh level, to > 400 copies/ml.

^cComparison between groups, Kruskal-Wallis and chi-square tests.

Table 3:

	Suppressed	Transiently viremic	Lasting rebound to low level ^a	Lasting rebound to high level ^b	P value ^c
Total number	235	110	62	17	
Difference in CD4 cell count from the start of regimen to end of study period [median (IQR)]					
Absolute ^d	170.0 (42.0–311.0)	205.5 (79.0–313.0)	190.5 (65.0–283.5)	75.0 (–56–149)	0.003
Percentage ^e	55.2 (11.1–119.9)	69.5 (25.9–174.1)	45.5 (23.5–87.3)	15.1 (–13.8–42.9)	0.002

IQR, interquartile range (Q1–Q3).

^aLow level, to 50–400 copies/ml.

^bHigh level, to > 400 copies/ml.

^cComparison between groups, Kruskal–Wallis test.

Table 4. Proportion of Patients Experiencing Viral Blips and Viral Load Amplitudes at Time of Blip

Study and Year	Patients with ≥ 1 Viral Blip/ Total Study N (%)	Median Viral Load (copies/mL) at Time of Blip	Blip Definition
García-Gascó et al, 2008	779/2720 (28.6)	110 ^a	VL 51–500 copies/mL preceded by 2 consecutive undetectable VL values within a 24-week or greater interval without subsequent virologic failure
Greub et al, 2002	490/2055 (23.8)	NA	VL 51–500 copies/mL preceded by 2 consecutive VL values < 50 copies/mL within a 24-week interval and a

			subsequent VL < 50 copies/mL
Sklar et al, 2002	122/448 (27.2)	96	VL 51–500 copies/mL preceded by 2 consecutive undetectable VL values within an 8-week or greater interval and a subsequent VL < 50 copies/mL
Sungkanuparph et al, 2005	128/380 (33.7)	140-144 ^b	VL 50–1000 copies/mL, preceded and followed by 1 VL < 50 copies/mL
Mira et al, 2002	37/330 (11.2)	130	VL of 50-1000 copies/mL preceded by 2 consecutive VL < 50 copies/mL and followed by at least 1 VL < 50 copies/mL
Havlir et al, 2001	96/241 (39.8)	NA	VL ≥ 50 copies/mL after achieving a VL < 200 copies/mL after 6 months on treatment and a subsequent VL < 50 copies/mL without evidence of subsequent virologic failure
Podsadecki et al, 2007	60/223 (26.9)	82	VL of 50–1000 copies/mL immediately preceded and

			followed by VL < 50 copies/mL
Martinez et al, 2005	8/43 (18.7)	350	VL > 50 copies/mL preceded by 3 consecutive VL < 50 copies/mL and a subsequent VL < 50 copies/mL without evidence of virologic failure
Nettles et al, 2005	8/10 (80) ^c	79	VL ≥ 50 copies/mL preceded by measurements < 50 copies/mL and followed by a return to below 50 copies/mL without a change in treatment
<p>VL indicates viral load; NA, data not available</p> <p>^a Mean viral load; low-level viral rebound (LLVR) episodes occurred in 22.5% of patients on triple nucleoside analogue reverse transcriptase inhibitor (nRTI)-regimens, 44% on nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-based regimens and 33.5% on protease inhibitor (PI)-based regimens.</p> <p>^b Range of median values depending on antiretroviral regimen, first blip only.</p> <p>^c Frequent VL testing (every 2-3 days) may have led to higher proportion of patient with blips (4 patients also experienced blips prior to study enrollment).</p>			

Table 5. Proportion of Patients With and Without Blips who Developed Virologic Failure

Study, Year	Virologic Failure in Patients with Viral Blips/ Total Study N (%)	Virologic Failure in Patients without Viral Blips/ Total Study N (%)	Virologic Failure Study Definition	Comments
García-Gascó et al 2008	66/655 (10.1)	NA	VL > 500 copies/mL after the LLVR episode	Rate of virologic failure has substantially diminished since 2001; older age and higher VL at the time of LLVR significantly associated with virologic failure
Sklar et al 2002	16/122 (13.1)	52/326 (16.0) ^a	Lasting rebound viremia of VL > 50 copies/mL following 2 consecutive VL < 50 copies/mL	Lasting rebound used as basis for virologic failure in this comparison
Mira et al, 2002	3/37 (8.1)	11/65 (16.9)	VL > 200 copies/mL for at least 2 consecutive visits	VL level not associated with subsequent failure
Havlr et al, 2001	10/96 (10.4)	20/145 (13.8)	2 consecutive VL > 200 copies/mL after suppression	Blip amplitude of > 200 copies/mL not predictive of virologic failure
Podsadecki et al 2007	9/60 (15.0)	21/137 (15.3)	2 consecutive VL = 50 copies/mL after suppression	
Martinez et al, 2005	0/8 (0)	0/35 (0)	2 consecutive VL > 200 copies/mL	All patients on new NNRTI-based regimen

Sungkanuparph et al, 2005	NA	NA	2 consecutive VL > 1000 copies/mL	Neither number of blips nor size of the blips affected the probability of virologic failure
Greub et al, 2002	NA	NA	1 VL > 500 copies/mL	7.6% of all patients developed virologic failure; amplitude of the initial viral rebound related to subsequent failure; blips associated with 2-fold increase in virologic failure
<p>VL indicates viral load (ie, HIV-1 RNA level); NA, data not available; LLVR, low-level viral rebound; NNRTI, nonnucleoside analogue reverse transcriptase inhibitor ^a 326 patients represents remaining cohort after excluding patients with transient LLVR</p>				