

Low-level HIV viremia: Definitions, predictors, mechanisms, and clinical outcomes

Question

- What are the factors associated with low-level HIV viremia?
- What are its possible mechanisms and clinical outcomes?

Key Take-Home Messages

- The definitions of optimal viral suppression, low-level viremia, blips, virologic failure, and recommended management approaches to low-level viremia vary greatly across studies and clinical guidelines.
- There is controversy regarding the clinical implications of persistently low HIV RNA levels that are between the lower limits of detection and <200 copies/mL in patients on antiretroviral therapy (ART) (1). Several studies support the supposition that virologic failure is more likely to occur in patients with viral load (VL) ≥ 200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL. However, other studies have suggested that detectable viremia at this low level (<200 copies/mL) or even lower (<50 copies/mL) can be predictive of virologic failure and can be associated with the evolution of drug resistance (1).
- The source(s) and mechanisms of persistent low-level HIV plasma viremia are still largely uncharacterized despite improved detection methods, but evidence suggests that it probably largely arises from clonally expanded CD4⁺ T-cells, although some contribution of ongoing viral replication cannot be excluded (2).

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- There is a dearth of clinical trials on the management of low-level viremia, and guidelines often reflect expert opinion (3).
- Low-level- and very-low-level viremia can be the result of multiple factors (including virologic factors, ART adherence, etc). It is often difficult to determine the exact cause or clinical significance. It is possible, though not confirmed, that persistent low-level- and very-low-level viremia may predict higher risk of virologic failure, morbidity and mortality.

The Issue and Why it's Important

After achieving virologic suppression of less than 50 copies/ml, most (more than half) of people living with HIV on ART maintain a residual HIV viremia at very low levels (1–10 copies/ml) (2, 4, 5). Among the patients who have achieved virologic suppression of less than 50 copies/ml, both transient and persistent increases in VL are frequently seen (4, 6). Blips, an isolated HIV RNA of at least 50 copies/mL that is immediately preceded and followed by virologic suppression, have been found in between 10 and 50% of people living with HIV (4, 6, 7). Low-level viremia, defined as two or more consecutive HIV RNA of at least 50 copies/mL, has an estimated prevalence of between 4 and 30% (4, 8, 9), although some unusually low prevalence of less than 1% has also been reported (10).

The clinical significance of low-level viremia remains unclear and is an area of particular clinical interest. Much of the challenge in interpreting the significance of low-level viremia comes from the discrepancies between various studies, including the lack of uniformity in definitions of low-level viremia and virologic failure (4, 11). Using a relatively expansive definition, low-level viremia between 200 and 1,000 copies/mL has consistently been associated with virologic failure, viral evolution, and the emergence of drug resistance (12, 13). However, questions remain about whether low-level viremia between 50–199 copies/mL and under 50 copies/mL, is associated with virologic failure and other potentially negative health outcomes.

This review summarizes various definitions of low-level viremia and related terms, as well as the current evidence on incidence, risk factors, and clinical outcomes of low-level viremia in people living with HIV and receiving ART. HIV elite controllers and mechanisms associated with viral suppression in this population are beyond the scope of this review.

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What We Found

The suppression of plasma HIV RNA concentration (VL) below the quantification limits of clinically accessible assays is a widely accepted indicator of successful ART (1, 14).

Some people on ART develop intermittent (i.e., viral blips) or persistent low-level viremia, which is usually defined as an HIV VL that is above the lower limit of detection of a specific assay (e.g., <20 or <50 copies/mL) but below the threshold for virologic failure (usually, but not always, defined as 200 copies/mL) (15). Recognition of very-low-level viremia is on the rise given the progressive decrease in the reported quantification limits of clinical assays, and is usually defined as HIV plasma VL of <50 copies/mL detected by clinical assays with quantification cut-offs of <50 copies/mL (3).

Actual rates of low- and very-low-level HIV viremia vary widely across studies due to differences in its definition, study designs, and VL assays used given the progressive decrease in their reported quantification limits (3). In recent years, the sensitivities of clinical assays available to diagnose low-level viremia have outpaced the understanding of their clinical consequences and access to reliable resistance assays necessary to optimize treatment decisions (3).

This review synthesizes literature regarding clinical, virologic, and immunologic consequences of low-level HIV viremia.

Definitions of low-level viremia and other related terms

The definitions of optimal viral suppression, low-level viremia, blips, virologic failure, and recommended management approaches to low-level viremia vary greatly across studies and clinical guidelines. A recent methodological review of 180 HIV randomized controlled trials that evaluated the definition of HIV virologic outcomes (such as virologic failure or virologic rebound) in the literature and factors associated with them found that studies use different measures to define virologic outcomes in HIV clinical trials. The use of VL thresholds ≤ 50 copies/mL appears to be associated with industry-funded studies and studies conducted in high-income countries (16). The same inconsistencies can be observed across clinical guidelines. Table 1 summarizes the latest versions of the five most widely used HIV treatment guidelines published by the following organizations:

- U.S. Department of Health and Human Services (DHHS) 2021 (1)
- International Antiviral Society–USA Panel 2020 (17)
- European AIDS Clinical Society (EACS) 2021 (14)
- British HIV Association (BHIVA) 2016 (18)
- World Health Organization (WHO) 2016 (19).

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Table 1. Summary of major guidelines for definitions and management of HIV viremia. Adapted from Ryscavage et al., 2014 (3), updated with 2021 data.

	U.S. Department of Health and Human Services (DHHS) 2021 (1)	International Antiviral Society–USA Panel 2020 (17)	European AIDS Clinical Society (EACS) 2021 (14)	British HIV Association (BHIVA) 2016 (18)	World Health Organization (WHO) 2016 (19)
Definition of optimal viral suppression	Virologic suppression: A confirmed HIV RNA level below the lower levels of detection of available assays. VL persistently below the level of detection (HIV RNA <20 to 75 copies/mL, depending on the assay used).	<50 copies/mL (implied).	Virological suppression: VL <50 copies/mL for at least 6 months.	Virological suppression: Achieving and maintaining a VL level <50 copies/mL.	A viral load below the detection threshold using viral assays.
Definition of low-level viremia	Confirmed detectable HIV RNA level <200 copies/mL.	Between 50 copies/mL and 200 copies/mL.	Not defined as low-level viremia, but VL > 50 and < 200 copies/mL implied.	Low-level viraemia: A persistent VL between 50-200 copies/mL.	50–1,000 copies/mL.
Definition of blips	After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression (VLs transiently detectable at low levels, typically HIV RNA <400 copies/mL).	An isolated increase in HIV RNA levels to <1,000 copies/mL with a return to undetectable levels while receiving ART.	Not defined.	Virological blip: After virological suppression, a single VL between 50 and 200 copies/mL followed by an undetectable result.	Intermittent low-level viraemia (50–1,000 copies/mL).

Table 1 (continued). Summary of major guidelines for definitions and management of HIV viremia. Adapted from Ryscavage et al., 2014 (3), updated with 2021 data.

	U.S. Department of Health and Human Services (DHHS) 2021 (1)	International Antiviral Society–USA Panel 2020 (17)	European AIDS Clinical Society (EACS) 2021 (14)	British HIV Association (BHIVA) 2016 (18)	World Health Organization (WHO) 2016 (19)
Definition of virologic failure	The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL (VL >200 copies/mL).	Virological failure: A confirmed HIV RNA level above 200 copies/mL on 2 consecutive measurements in an individual receiving ART.	Incomplete suppression: VL > 50 copies/mL at 6 months after starting therapy in those not previously on ART. In those with very high baseline HIV-VL (> 100,000 copies/mL), achieving viral suppression may take longer than 6 months. Rebound: confirmed HIV-VL > 50 copies/mL in those with previously undetectable HIV-VL.	Virological failure: incomplete virological response after commencing treatment or evidence of confirmed virological rebound to >200 copies/mL. Incomplete virological response: two consecutive VL >200 copies/mL after 24 weeks without ever achieving VL <50 copies/mL. Virological rebound: failure to maintain a VL below the limit of detection (ordinarily <40–50 copies/mL) on two or more consecutive occasions.	Virological (viral) failure: VL above 1,000 copies/mL based on two consecutive VL measurements in 3 months, with adherence support following the first viral load test.
Management of low-level viremia	HIV RNA above the lower limits of detection and <200 copies/mL: do not typically require a change in treatment. Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low. Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future.	Patients with intermittent or persistent low-level viremia between 50 copies/mL and 200 copies/mL should be assessed for treatment adherence, tolerability, and toxicity; however, changing ART regimens is not recommended unless ART toxicity or intolerability are identified.	If VL > 50 and < 200 copies/mL: Check for adherence, reinforce adherence. Check VL 1 to 2 months later. If genotype shows no resistance mutations: maintain current ART if it contains INSTI with high barrier to resistance (BIC, DTG) or PI/b, otherwise monitor carefully.	A single VL 50–200 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern. It should necessitate clinical vigilance, adherence reinforcement, check for possible interactions, and repeat testing within 2–6 weeks depending on ART regimen. A single VL >200 copies/mL to be investigated further, including a rapid re-test +/- genotypic resistance test, as it may be indicative of virological failure. In the context of low-level viraemia or repeated viral blips, resistance testing to be attempted.	Management defined only for virologic failure (a threshold of 1,000 copies/mL) as the risk of HIV transmission and disease progression is very low when VL is <1,000 copies/mL, and below this threshold, viral blips or intermittent low-level viraemia (50–1,000 copies/mL) can occur during effective treatment but have not been associated with an increased risk of treatment failure.

The U.S. DHHS 2021 Guidelines define low-level viremia as a confirmed detectable HIV RNA level <200 copies/mL, whereas the inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL is considered a virologic failure (1). The guidelines point out that patients with detectable VLs comprise a heterogeneous group of individuals with different ART exposure histories, degrees of drug resistance, durations of virologic failure, and levels of plasma viremia (1). Management strategies should be individualized, and the first steps for all patients with detectable VLs are to confirm the level of HIV viremia and assess and address adherence and potential drug-drug interactions (including interactions with over-the-counter products and supplements) and drug-food interactions (1). The DHHS guidelines indicate that patients who have HIV RNA levels between the lower limits of detection and 200 copies/mL do not typically require a change in treatment (1). Although there is no consensus on how to manage these patients, the risk that resistance will emerge is believed to be relatively low (1). Therefore, these patients should continue their current regimens and have HIV RNA levels monitored at least every 3 months to assess the need for changes to ART in the future (1). In contrast, those with HIV RNA levels persistently between ≥ 200 copies/mL and <1,000 copies/mL, often develop drug resistance, particularly when HIV RNA levels are >500 copies/mL (1).

In patients with undetectable VL or low-level viremia, the U.S. DHHS 2021 Guidelines recommendations for using drug-resistance assays suggest that HIV-1 proviral DNA resistance assays may be useful, where HIV RNA genotypic assay is unlikely to be successful (1). This test may provide information about previously circulating resistant viral variants that are archived within proviral DNA (1). These assays may miss some or all prior resistance mutations that have occurred within the viral quasi-species, and therefore they should be interpreted with caution (1). The clinical utility of HIV-1 proviral DNA assays has not been fully determined (1).

International Antiviral Society–USA Panel 2020 guidelines provide a similar definition of low-level viremia (between 50 copies/mL and 200 copies/mL) and suggest that these patients to be assessed for treatment adherence, tolerability, and toxicity; however, changing ART regimens is not recommended unless ART toxicity or intolerability is identified (17).

The European AIDS Clinical Society (EACS) 2021 Guidelines do not provide a definition of low-level viremia but distinguish between incomplete suppression, defined as VL > 50 copies/mL at 6 months after starting ART, and rebound, defined as a confirmed VL > 50 copies/mL in those with previously undetectable VL (14). In cases when VL > 50 and < 200 copies/mL, EACS recommends checking for adherence and reinforcing it, checking VL one to two months later, and if genotyping shows no resistance mutations, maintaining current ART if it contains either integrase strand transfer inhibitors (INSTI) with high barrier to resistance such as bictegravir (BIC),

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dolutegravir (DTG), or boosted protease inhibitors (PI/b), otherwise monitoring carefully (14).

British HIV Association (BHIVA) 2016 guidelines consider a persistent VL between 50–200 copies/mL a low-level viremia (18). This is in contrast to a virologic blip—a single VL between 50 and 200 copies/mL—followed by an undetectable result after virologic suppression (18). Failure to maintain a VL below the limit of detection (ordinarily <40–50 copies/mL) on two or more consecutive occasions is considered a virologic rebound (18).

According to BHIVA, low-level viremia is observed in up to 8% of individuals and, when compared to viral suppression to <50 copies/mL, is associated with an increased risk of virologic failure and resistance (18). The likelihood of re-suppression after LLV is greater for lower magnitudes of viraemia (18). BHIVA considers it uncertain whether low-level viremia <200 copies/mL always confers independent risks, as viremia at this level may on occasion reflect assay variation. BHIVA recognizes that low-level viremia is associated with resistance that may be associated with the magnitude of low-level viremia (18).

BHIVA suggests that a single VL 50–200 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern (18). But it should necessitate clinical vigilance, adherence reinforcement, checking for possible interactions, and repeat testing within 2–6 weeks depending on ART regimen (18). BHIVA also recommends that resistance testing should be considered, where feasible, in all cases of low-level viremia on treatment (18). Where resistance is detected, regimens should be modified appropriately (18). In the absence of clear data, the writing group believes persistent low-level viremia on a low-genetic barrier regimen (including non-nucleoside reverse transcriptase inhibitor [NNRTI]-based or integrase inhibitor-based therapy), even in the absence of detectable resistance, warrants prompt regimen change (18).

The World Health Organization (WHO) 2016 definition of virologic (viral) failure requires a persistently detectable viral load exceeding 1,000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of using ART (19). The WHO notes that although the optimal threshold for defining viral failure and for switching ART regimens has not been established, it recommends a threshold of 1,000 copies/mL based on the fact that the risk of HIV transmission and disease progression is very low when VL is lower than 1,000 copies/mL, and that below this threshold, viral blips or intermittent low-level viremia (50–1,000 copies/mL) can occur during effective treatment but have not been associated with an increased risk of treatment failure (19).

WHO guidelines inform clinical management in most resource-limited settings, and recent studies from these settings suggest

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that lowering the threshold for switching to second-line ART to 100 copies/mL led to a higher proportion of participants with low-level viremia achieving viral suppression (<50 copies/mL) (20, 21). These studies support a lower threshold for defining virologic failure and switching to second-line ART in future WHO guidelines (20, 21) as well as incorporating of provisions for management of low-level viremia in them (22).

Mechanisms of low-level viremia

Two main pathophysiological hypotheses have been proposed to explain low-level viremia: ongoing viral replication in sanctuary sites (reservoirs) with suboptimal drug penetration, viral production by the activation of HIV-infected cells, or both (2, 23). In other words, the longstanding debate is whether low-level viremia on ART results from ongoing, complete cycles of viral replication, or is from clonally expanded infected T cells that produce virions but that do not infect new cells because they are protected by antiretrovirals (2).

As there have been studies of viral replication on ART due to low drug penetration and exclusion of immune cells in anatomical sanctuary sites (such as the lymph nodes), some residual low-level viral replication on ART cannot be definitively ruled out (2). Nevertheless, the weight of the evidence argues against viral replication as the major source of persistent low-level viremia (2, 24). The recent discovery by multiple groups that most of the inducible, infectious virus comes from clonally expanded T-cells argues for cellular proliferation and against ongoing viral replication as the major mechanism for persistence of HIV-1 reservoirs (2).

Potential predictors of low-level viremia

Several potential risk factors for low-level viremia and very-low-level viremia have been investigated. It appears that no single factor is determinative in all cases, and it is likely that most cases are multifactorial (3).

Stage of HIV infection prior to ART initiation

Among 1,158 patients receiving their first ART in two randomized clinical trials, pretreatment VL of ≥ 6 log₁₀ copies/mL (1 million copies/mL) was associated with a 2.2-fold-increased risk of persistent viremia of >50 and <1,000 copies/mL (8).

An Italian study of 44 multidrug-experienced patients with undetectable levels of HIV RNA for at least 2 years under raltegravir-based regimens found a potential influence of the time interval between HIV diagnosis and ART initiation on levels of residual viremia: among patients equally suppressed for VL, those who had a longer interval between HIV diagnosis and start of the first ART

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had higher levels of residual viremia and were less likely to have HIV RNA levels below 2.5 copies/mL, compared to patients who started ART within one year of HIV diagnosis (25).

Similarly, the Austrian HIV Cohort Study data demonstrated a higher risk for low-level viremia (<200 copies/mL) in patients with a higher VL before ART initiation: aOR 4.19 (95% CI 2.07–8.49) and aOR (95% CI): 2.52 (1.23–5.19) for >99.999 copies/mL and for 10.000–99.999 copies/mL (compared to those with <9.999 copies/mL), respectively (26).

In some other studies, having very-low-level viremia compared to suppression below the assay detection limit (which varied between studies) was associated with higher pre-ART VL (27, 28).

In contrast, other studies observed no association between pre-treatment plasma VL and risk of persistent viremia of >50 copies/mL (3).

Viral blips

Blips are usually defined in the context of effective treatment as a single, measurable HIV RNA level, typically <200 copies/mL, that is followed by a return to a VL below the limit of detection or quantification (1). Most blips likely represent normal biological fluctuation (i.e., variation around a mean undetectable VL) or laboratory artifact and not inadequate adherence (1). One of the clinical challenges with blips is that they can only be defined retrospectively once the VL has returned to a suppressed value (1).

Several studies have examined the risk of virologic failure among patients experiencing viral blips, using different cut-offs to define virologic failure (3). For example, information collected through the Canadian Observational Cohort (CANOC) collaboration found an increased risk of viral rebound (two consecutive VLs of >50 copies/mL at least 30 days apart or a single VL of $\geq 1,000$ copies/mL) among patients with viral blips of 500 to 999 copies/mL, but not among those with viral blips of 50 to 499 copies/mL (hazard ratio [HR], 2.70; $P = 0.002$) (34).

ART adherence

Several studies investigated a possible role that inadequate ART adherence may play in low-level viremia. A study from Colorado identified an association of low-level viremia (VL between 20 and 200 copies/mL) and a decrease in cumulative ART adherence measured using tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) (15). In a large Italian study of 2,789 patients, reduced ART adherence was associated with very-low-level residual viremia (<50 copies/mL), which could reflect new rounds of HIV replication (29). However, a detectable HIV RNA (>3 copies/mL) could also be observed in patients with optimal ART adherence (>95%), indicating

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additional mechanisms resulting in HIV persistence (29).

Data of 15 patients with low-level viremia (≥ 2 VL measurements between 50 and 500 copies/mL) from four French university hospital indicated that poor long-term ART adherence, estimated by prescription refills, was strongly associated with low-level viremia (30).

Clinical significance of low-level viremia

Antiretroviral drug resistance

Antiretroviral drug resistance is well documented in patients with a viremia level of $< 1,000$ copies/mL (3), but the reported prevalence varies depending on ART experience, virologic suppression/failure, duration of viremia, and treatment regimen (8, 12, 31-35). In one of the largest studies ($n = 1,001$), genotyping of clinical samples in the UK revealed at least one drug resistance mutation in 60% and 72% of samples, with VL of < 300 copies/mL and 300 to 999 copies/mL, respectively (32). In British Columbia, 38 (19%) of 196 treatment-naive patients without baseline resistance had at least one drug resistance mutation at their first low-level viremia of 50 to 1,000 copies/mL (35). Almost all of the drug resistance mutations affected nucleoside reverse transcriptase inhibitors (NRTIs) and/or NNRTIs, and none affected a boosted protease inhibitor (35).

There is a trend toward greater resistance with higher VL during low-level viremia (8, 35, 36). In one study, new drug resistance mutations were detected in 0% (0 of 10 patients) with a maximum VL of 51 to 100 copies/mL, compared with 38% (5 of 13) with a VL of 101 to 200 copies/mL, and 48% (15 of 31), with a maximum VL of 200 to 1,000 copies/mL (8). Attainment of VL ≤ 50 copies/mL at any time during low-level viremia was negatively associated with new mutations ($P = 0.006$), whereas a VL increase to ≥ 1000 copies/mL was positively associated ($P = 0.009$) (8). In a French study of 57 patients with persistent low-level viremia defined as at least two consecutive VLs between 21 and 200 copies/mL, none of the participants developed resistance to their current ART (23).

In the British Columbia cohort, the median VLs in patients who evolved resistance and those who did not, were 472 copies/mL and 369 copies/mL ($P = 0.067$), respectively (35). It was observed that the prevalence of resistance increased at higher VL strata at low-level viremia. Only 5% of patients ($n = 2$) with 50–249 copies/mL had resistance, whereas 24% ($n = 22$), 17% ($n = 7$), and 30% ($n = 7$) had resistance at 250–499, 500–749 and 750–999 copies/mL, respectively ($P = 0.041$) (35).

In a Belgian study, long-term follow-up (median 4.7 years) of 23 patients on ART who failed to obtain durable suppression of the VL revealed that long episodes of persistent low-level-viremia

31. Delaugerre C, Gallien S, Flandre P, Mathez D, Amarsy R, Ferret S, et al. Impact of low-level-viremia on HIV-1 drug-resistance evolution among antiretroviral treated-patients. *PLoS ONE*. 2012;7(5):e36673.
32. Mackie NE, Phillips AN, Kaye S, Booth C, Geretti AM. Antiretroviral drug resistance in HIV-1-infected patients with low-level viremia. *Journal of Infectious Diseases*. 2010;201(9):1303-7.
33. Prosperi MC, Mackie N, Di Giambenedetto S, Zazzi M, Camacho R, Fanti I, et al. Detection of drug resistance mutations at low plasma HIV-1 RNA load in a European multicentre cohort study. *Journal of Antimicrobial Chemotherapy*. 2011;66(8):1886-96.
34. Kao SW, Liu ZH, Wu TS, Ku SW, Tsai CL, Shie SS, et al. Prevalence of drug resistance mutations in HIV-infected individuals with low-level viraemia under combination antiretroviral therapy: An observational study in a tertiary hospital in Northern Taiwan, 2017-19. *Journal of Antimicrobial Chemotherapy*. 2021;76(3):722-8.
35. Gonzalez-Serna A, Min JE, Woods C, Chan D, Lima VD, Montaner JS, et al. Performance of HIV-1 drug resistance testing at low-level viremia and its ability to predict future virologic outcomes and viral evolution in treatment-naive individuals. *Clinical Infectious Diseases*. 2014;58(8):1165-73.

fluctuating around 50 copies/mL under boosted PI-based regimens rarely resulted in drug resistance (37).

Virologic failure

There is a large body of evidence indicating an increased risk of virologic failure in patients with persistent viremia of 50 to 1,000 copies/mL (3). For example, two large Canadian studies evaluated the impact of persistent low-level viremia on the subsequent risk of virologic failure, defined in both studies as a VL of >1000 copies/mL (38, 39):

The study of 1,860 participants from Montreal compared the cumulative incidence of subsequent virologic failure in patients receiving ART for at least 12 months by following four persistence categories (<50, 50–199, 200–499, and 500–999 copies/mL) for six, nine, or 12 months (39). The cumulative incidence of virologic failure one year after having maintained a low-level viremia for six months was 22.7% for 50–199 copies/mL, 24.2% for 200–499 copies/mL, and 58.9% for 500–999 copies/mL, compared with 6.6% for an undetectable VL (<50 copies/mL) (39). Even after adjustment for potential confounders, a persistent low-level viremia of 50–199 copies/mL for six months doubled the risk of virologic failure (HR, 2.22; 95% CI, 1.60–3.09), compared with undetectable VLs for the same duration, and similar results have been found for persistent low-level viremia of 9 or 12 months (39).

An analysis of 1,702 patients from British Columbia revealed that patients experiencing their first episode of low-level viremia while on ART were up to three times more likely to experience subsequent virologic failure if they had emergent drug resistance at the time of low-level viremia (38). Virologic failure followed a “dose-dependent” response in relationship to the genotypic susceptibility scores (GSS) values, with progressively decreasing GSS associated with increasing risk of subsequent virologic failure (38). The GSS predicted virologic failure in a linear fashion even when the VL was 50 to 250 copies/mL (38).

The HIV Research Network (HIVRN) in the U.S. analyzed data from 2,795 patients and found that low-level viremia between 201 and 500 copies/mL as well as between 51 and 200 copies/mL was strongly associated with virologic failure, particularly among ART-experienced patients (4).

The U.S. Military HIV Natural History Study (NHS) of 2,006 participants came to similar results, finding that persistent low-level viremia (VL of 50–199 copies/mL on $\geq 25\%$ of measurements, HR, 3.46), as well as high-level viremia (VL of 200–1,000 copies/mL HR, 2.29) were both associated with virologic failure, defined as a confirmed VL ≥ 200 copies/mL or any VL >1000 copies/mL (40).

Similarly, an analysis of 2,374 patient data from the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO3 Aquitaine

36. von Wyl V, Yerly S, Böni J, Shah C, Celleraï C, Klimkait T, et al. Incidence of HIV-1 drug resistance among antiretroviral treatment-naïve individuals starting modern therapy combinations. *Clinical Infectious Diseases*. 2012;54(1):131-40.
37. Vancoillie L, Mortier V, Demecheleer E, Schauvliege M, Vandekerckhove L, Vogelaers D, et al. Drug resistance is rarely the cause or consequence of long-term persistent low-level viraemia in HIV-1-infected patients on ART. *Antiviral Therapy*. 2015;20(8):789-94.
38. Swenson LC, Min JE, Woods CK, Cai E, Li JZ, Montaner JS, et al. HIV drug resistance detected during low-level viraemia is associated with subsequent virologic failure. *AIDS*. 2014;28(8):1125-34.
39. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: Results from 12 years of observation. *Clinical Infectious Diseases*. 2013;57(10):1489-96.
40. Joya C, Won SH, Schofield C, Lalani T, Maves RC, Kronmann K, et al. Persistent low-level viremia while on antiretroviral therapy is an independent risk factor for virologic failure. *Clinical Infectious Diseases*. 2019;69(12):2145-52.

Cohort, 205 (8.6%) of which experienced at least one episode of low-level viremia (50–199 copies/mL), found that persistent low-level viremia between 50–199 copies/mL was associated with virologic failure among ART-experienced patients (41). The authors suggested that low-level viremia between 50–199 copies/mL in ART-experienced patients should lead, after assessing adherence and checking for drug interactions, to a closer monitoring and to considering ART optimization (41).

On the other hand, the large Antiretroviral Therapy Cohort Collaboration-study (ART-CC) (data from 18 cohorts in Europe and North America representing 17,902 patients) found that the association between low-level viremia of 50–199 copies/mL and virologic failure was weak and not statistically significant (aHR 1.38, 95% CI 0.96–2.00), whereas the association between viremia of 200–499 copies/mL and virologic failure was strong (aHR 3.97, 95% CI 3.05–5.17) (42).

The Swedish nationwide InfCare register data also found that the incidence of virologic failure was increased in patients with low-level viremia ≥ 200 copies/mL, but not for those with low-level viremia < 200 copies/mL virologic failure (43). Similarly, the Swiss HIV Cohort data of 9,972 patients, show that predictors of virologic failure were previous VF (aOR 35, 95%CI 3.8, 315), unboosted PI-based (aOR 12.8, 95%CI 1.7, 96) or NRTI-only combinations (aOR 115, 95%CI 6.8, 1,952), and VLs > 200 during persistent low-level viraemia (aOR 3.7, 1.1, 12), but no virologic failure occurred in patients with persistent very-low-level viremia (21–49 copies/ml; n=26) (44).

Another study (from Boston, U.S., n=778) has reported increased risk of rebound to > 50 , > 200 , > 400 copies/mL but importantly, not to $> 1,000$ copies/mL or higher, among those with detectable viremia (< 48 copies/mL) (45). The majority of the rebounds of > 200 copies/mL were blips and resistance rarely emerged, making the significance of these events unclear (45).

Very-low-level viremia

Increasingly, VL assays have quantification cut-offs lower than 50 copies/mL. Thus, individuals may have persistent viremia of > 20 or > 40 copies/mL but < 50 copies/mL, depending on the assay used. Some studies specifically investigated the impact of this very-low-level viremia on subsequent virologic failure, with some conflicting results (27, 28, 45–48).

In a UK study, subjects were stratified into VL 40–49 copies/mL, < 40 copies/mL with RNA detected, and < 40 copies/mL with no RNA detected (28). The study found that compared to individuals with VL < 40 copies/mL and no detected RNA, having viremia of 40–49 copies/mL increased the risk of rebound to > 50 copies/mL by 4.67-fold, while having detectable RNA at < 40 copies/mL increased the risk by 1.97-fold. The risk of rebound to > 400 copies/mL was

41. Vandenhende MA, Perrier A, Bonnet F, Lazaro E, Cazanave C, Reigadas S, et al. Risk of virological failure in HIV-1-infected patients experiencing low-level viraemia under active antiretroviral therapy (ANRS C03 cohort study). *Antiviral Therapy*. 2015;20(6):655–60.
42. Antiretroviral Therapy Cohort C, Vandenhende MA, Ingle S, May M, Chene G, Zangerle R, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. 2015;29(3):373–83.
43. Elvstam O, Medstrand P, Yilmaz A, Isberg PE, Gisslen M, Bjorkman P. Virological failure and all-cause mortality in HIV-positive adults with low-level viremia during antiretroviral treatment. *PLoS ONE*. 2017;12(7):e0180761.
44. Boillat-Blanco N, Darling KE, Schoni-Affolter F, Vuichard D, Rougemont M, Fulchini R, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antiviral Therapy*. 2015;20(2):165–75.
45. Henrich TJ, Wood BR, Kuritzkes DR. Increased risk of virologic rebound in patients on antiviral therapy with a detectable HIV load < 48 copies/mL. *PLoS ONE*. 2012;7(11):e50065.

increased by 6.91-fold and 2.88-fold, respectively (28) .

In a Spanish study, after 1 year of follow-up, patients on ART with a baseline VL of <20 copies/mL showed significantly lower odds of virologic rebound to two consecutive VLs of >50 copies/mL compared to those with baseline VLs of 20 to 39 and 40 to 49 ($P < 0.001$) (46). Another Spanish study ($n=326$) demonstrated that compared to the patients with undetectable VL, those with at least three consecutively detected, but not quantified, HIV-RNA values (<20 copies/mL) experienced higher risk of virologic failure (HR, 3.81) (7). Moreover, those with at least three consecutively detected, but not quantified, HIV-RNA determinations (<20 copies/mL) showed a higher probability of virologic rebound with >200 copies/mL (33.7% at 24 and 60 months versus <5% for other HIV-RNA values; HR, 6.943) (7).

An Italian study also demonstrated that a HIV RNA level >3 copies/mL was highly predictive of virologic failure and that a linear relationship existed between the residual viremia and the risk of virologic failure (27). A retrospective analysis on another large sample ($n=1,055$ patients) from Italy also confirmed that the undetectability of HIV RNA (“Target Not Detected”) was associated with a lower risk of virologic rebound in the following two years as compared to the other two degrees of low-level viremia (less than 20 copies/mL and between 20 and 50 copies/mL) .

Conversely, in another Italian study of 739 participants compared the risk of virologic failure of patients with residual viremia (1–49 copies/mL) to that of aviremic patients (<1 copy/mL) (47). In this study, residual viremia was not associated with virologic rebound during 1 year of follow-up (47).

A French study compared patients with VL values <20 copies/mL with those between 20 and 50 copies/mL (48). The study found no evidence of association between residual viremia (between 20 and 50 copies/mL) and virologic rebound over 1 year of follow-up, and the proportion of patients experiencing virologic failure was not different between the two groups (48).

In a study of a large urban HIV clinic in the U.S., the majority of patients with very-low-level viremia (VL between 20 and 50 copies/mL) subsequently achieved virologic suppression (VL <20 copies/mL) after 1 year of follow-up without changes in ART (49). Less than 5% of patients with very-low-level viremia experienced overt virologic failure (VL > 200 copies/mL) in one year of follow-up but none had documented HIV viral resistance (49). The authors concluded that very-low-level viremia does not necessarily predict virologic failure and should not prompt more frequent clinic visits or ART regimen changes (49).

Similarly, in a large Spanish study, the occurrence of very-low-level viremia (VL 20–50 copies/mL) rather than maintaining full

46. Álvarez Estévez M, Chueca Porcuna N, Guillot Suay V, Peña Monge A, García García F, Muñoz Medina L, et al. Quantification of viral loads lower than 50 copies per milliliter by use of the Cobas AmpliPrep/Cobas TaqMan HIV-1 test, version 2.0, can predict the likelihood of subsequent virological rebound to > 50 copies per milliliter. *Journal of Clinical Microbiology*. 2013;51(5):1555-7.
47. Gianotti N, Galli L, Racca S, Salpietro S, Cossarini F, Spagnuolo V, et al. Residual viraemia does not influence 1 year virological rebound in HIV-infected patients with HIV RNA persistently below 50 copies/mL. *Journal of Antimicrobial Chemotherapy*. 2012;67(1):213-7.
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49. Helou E, Sheno S, Kyriakides T, Landry ML, Kozal M, Barakat LA. Characterizing patients with very-low-level HIV viremia: A community-based study. *Journal of the International Association of Providers of AIDS Care*. 2017;16(3):261-6.
50. Teira R, Vidal F, Munoz-Sanchez P, Geijo P, Viciano P, Ribera E, et al. Very low level viraemia and risk of virological failure in treated HIV-1-infected patients. *HIV Medicine*. 2017;18(3):196-203.

suppression at < 20 copies/mL was not associated with virologic failure (two consecutive VLs > 200 copies/mL) (50).

In the absence of clear data, the writing group of the British HIV Association guidelines believes that no treatment modification is required for individuals with detectable viremia below 50 copies/mL (18).

Morbidity and mortality

Some studies found no association between low-level viremia (<400 copies/mL) and AIDS progression and/or overall mortality. For example, data from 18 cohorts in Europe and North America, found that low-level viremia of either 50–199 copies/mL or 200–499 copies/mL were not associated with AIDS event/death (aHR 1.19, 95% CI 0.78–1.82; and aHR 1.11, 95% CI 0.72–1.71, respectively) (42).

Similarly, the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM) in the U.S. found little association between low-level viremia (<400 copies/mL) and inflammation markers (51); data from the large ATHENA cohort from the Netherlands showed that low-level viremia (<400 copies/mL) was not associated with non-AIDS diseases (52); the Swedish nationwide infCare register data found no association between low-level viremia (<1,000 copies/mL) and cancer incidence (53) or inflammation markers (54).

On the other hand, the same Swedish nationwide infCare register data found that compared with viral suppression (<50 copies/mL), low-level viremia (50–999 copies/mL), was associated with increased mortality (aHR 2.2) (55). This association was also observed for low-level viremia 50–199 copies/mL (aHR 2.2), but was not statistically significant for low-level viremia 200–999 copies/mL (aHR 2.1). Low-level viremia 50–999 copies/mL was not linked to increased risk of AIDS or serious non-AIDS events, but in subanalysis, low-level viremia 200–999 copies/mL was associated with serious non-AIDS events (aHR, 2.0) (55).

In a large Spanish study of 5,986 participants there were no observed differences in the low-level viremia of 50–199 copies/mL and no low-level viremia subgroups in either AIDS events or death (9). At the same time, VL of 200–499 copies/mL was strongly associated with a higher risk of both AIDS events and death (aHR, 2.89; 95% CI 1.41 to 5.92) and virologic failure (aHR, 3.25; 95% CI: 1.77 to 5.99) (9).

Other investigators have observed a correlation between cumulative plasma HIV exposure over time and both AIDS and non-AIDS morbidity and mortality (56). Viremia copy-years, a measure of cumulative plasma HIV burden, demonstrated prognostic value for all-cause mortality independent of traditional, clinically relevant cross-sectional VL measures and time-updated CD4+ T-lymphocyte count, suggesting that cumulative HIV replication causes harm independent of its effect on the degree of immunodeficiency (56).

51. Eastburn A, Scherzer R, Zolopa AR, Benson C, Tracy R, Do T, et al. Association of low level viremia with inflammation and mortality in HIV-infected adults. *PLoS ONE*. 2011;6(11):e26320.
52. Zhang S, van Sighem A, Kesselring A, Gras L, Smit C, Prins JM, et al. Episodes of HIV viremia and the risk of non-AIDS diseases in patients on suppressive antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*. 2012;60(3):265-72.
53. Elvstam O, Marrone G, Medstrand P, Treutiger CJ, Svedhem V, Gisslen M, et al. Associations between plasma human immunodeficiency virus (HIV) ribonucleic acid levels and incidence of invasive cancer in people with HIV after initiation of combination antiretroviral therapy. *Open Forum Infectious Diseases*. 2021;8(6):ofab131.
54. Elvstam O, Medstrand P, Jansson M, Isberg PE, Gisslen M, Bjorkman P. Is low-level HIV-1 viraemia associated with elevated levels of markers of immune activation, coagulation and cardiovascular disease? *HIV Medicine*. 2019;20(9):571-80.
55. Elvstam O, Marrone G, Medstrand P, Treutiger CJ, Sonnerborg A, Gisslen M, et al. All-cause mortality and serious non-AIDS events in adults with low-level human immunodeficiency virus viremia during combination antiretroviral therapy: Results from a Swedish nationwide observational study. *Clinical Infectious Diseases*. 2021;72(12):2079-86.
56. Mugavero MJ, Napravnik S, Cole SR, Eron JJ, Lau B, Crane HM, et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. *Clinical Infectious Diseases*. 2011;53(9):927-35.

These results should be interpreted with caution, as any impact on morbidity and mortality is likely to be modest and require a long period of follow-up and a large number of participants in order to be detected (3). In addition, the definition of low-level viremia and its subgroups as well as study methodologies vary greatly across studies. For example, the large ATHENA cohort study in the Netherlands found no increased risk of non-AIDS disease associated with low-level viremia compared to that associated with viral suppression, but 75.8% of 3,104 episodes of low-level viremia consisted of a single VL measurement, only making it difficult to distinguish between blips and low-level viremia (3, 52).

Factors That May Impact Local Applicability

Studies and guidelines use widely different and changing definitions of low-level viremia and related concepts, such as blips, virologic rebound, virologic failure. The use of VL thresholds that are lower than 50 copies/mL appears to be associated with industry-funded studies and studies conducted in high-income countries, but this is not always the case either, making the comparisons and generalizations of the evidence difficult. In many cases, evidence appears to be contradictory, and clinical guidelines are sometimes based on expert opinion.

What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) using a combination of text term HIV and terms (low level viremia or low viremia or [low adj2 replication] or low-level viremia or low level viraemia) in titles or abstracts. Searches were conducted on November 17, 2021 and results limited to English articles published from 2010 to present. Studies from low- and middle-income countries were excluded. Reference lists of identified articles were also searched. Google (grey literature) searches using different combinations of these terms were also conducted. The searches yielded 318 references from which 56 were included.