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REVIEW

HIV: how to manage low-level viraemia in people living with HIV

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Abstract

Background: People living with HIV (PLWH) and receiving antiretroviral therapy (ART) have a goal of achieving and maintaining viral suppression; however, low-level viraemia (LLV) (HIV-RNA viral load levels of 50–999 copies/mL) persists in certain patients despite consistent medication adherence, lack of drug interactions and no genotypic resistance. This is a narrative review of the growing evidence of LLV in PLWH to determine risk factors and ART management strategies and to discuss the implications of LLV on the development of future virological failure.

Methods: A systematic, comprehensive literature search was completed in the English language using PubMed, Google Scholar and bibliography review to gather information about LLV in PLWH between July 2014 and June 2021. The following keywords were used as search terms: "low-level viremia", "HIV", "viral blip", "intensification", "genotyping", "adherence" and "resistance."

Results: Of 66 studies examined, 39 were analysed and included in this review. All trials included were published between 2014 and 2021. Eleven studies assessed risk factors for LLV. Identified risk factors were low $CD4^+$ T cell nadir counts at baseline, higher baseline viral load measurements, medication non-adherence, non-nucleoside reverse transcriptase inhibitor use and others. Three studies assessed genotyping and concluded that the interpretation of both historical RNA genotype resistance testing and current proviral DNA genotype resistance testing in patients with LLV is appropriate. Seven studies were evaluated and determined that modifying or intensifying ART regimens resulted in decreased incidence of virological failure.

Conclusion: This compilation of reviewed data gives a framework for the management of PLWH with LLV. Currently, there are no clear or definitive treatment directions for LLV provided in guidelines. Complicating this topic further is the unclear and varying definitions of LLV. Future research is needed on this topic but patients presenting with LLV should have their medication adherence assessed, drug interactions checked and ART intensified, where appropriate.

Keywords: ART, genotyping, HIV, low-level viraemia, risk factors.

Citation

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Introduction

HIV is a highly transmissible disease that can lead to many complications at both the individual and population health levels if left untreated and undiagnosed. Globally, an estimated 38 million people are living with HIV/AIDS in 2019.[1] It is estimated that 1.7 million people, globally, acquired HIV in 2019, demonstrating a reduction of 23% from 2010 data.[1] An estimated 36,400 new cases were recorded in 2018 alone in the United States. Of the 1.2 million people living with HIV (PLWH) in the United States, 1 in 7 remain unaware and need testing followed by treatment. HIV disproportionately affects Black and Latino ethnicities, among other racial minorities.[2] Men who have sex with men (MSM) or bisexual men are at higher risk for contracting HIV infection.[3]

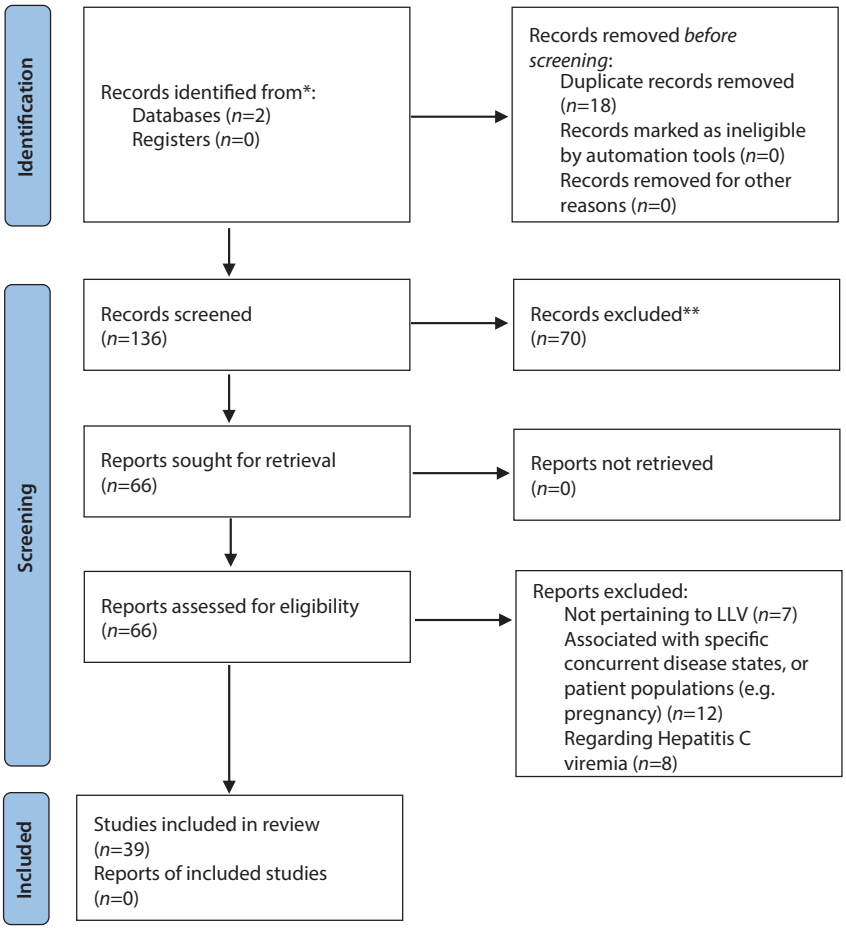
HIV infection treatment options have advanced significantly and rapidly. With this knowledge comes expanding questions on the efficacy of such treatments and proper algorithms for optimal patient safety and adequate viral suppression (VS). Antiretroviral therapy (ART) is the mainstay HIV treatment with proven efficacy demonstrated by achieving an undetectable viral load defined as less than 50 HIV-RNA copies/mL.[4] Often, more than one ART is combined to achieve and maintain VS and reduce the risk of HIV transmission.

VS levels are clearly defined, whereas persistent low-level viraemia (LLV) that is detectable is not. Most definitions of LLV range from >50 to 999 copies/mL.[5] Managing patients with LLV remains challenging, and the best strategy is unclear. LLV is often subcategorized into very-LLV (VLLV, less than 20 copies/mL) due to progress in technological abilities to detect viral loads.[6] LLV is hypothesized to exist from continued viral replication in sanctuary sites within the body that are unsuccessfully reached by ART or by potentially infected latent cells being stimulated to release HIV.[6] Risk factors for the development of LLV have been studied but remain inconclusive and are likely to be multifactorial.[6] Respected and followed treatment guidelines differ in their strategy to manage patients with LLV. It is important to distinguish LLV from a viral blip or drug resistance. A viral blip is detectable viraemia that is preceded and followed by VS.[6] The objective of this manuscript is to provide a contemporary narrative review of studies using modern ART in the management of patients with LLV and provide consensus evidence on the best approach and clinical consequences of LLV.

Methods

A systematic, comprehensive literature search was completed in the English language using PubMed, Google Scholar and bibliography review to gather information about LLV in PLWH. The following keywords were used: "low-level viremia", "HIV", "viral blip", "intensification", "genotyping", "adherence" and "resistance". Filters included July 2014 to June 2021 due to the most recent LLV review article being in July of 2014 with older antiretrovirals being the cornerstone of ART.[7] Articles were excluded if they did not specifically discuss LLV implications in HIV and if they included any persons under the age of 18; only articles in English were included in this study (Figure 1).

Figure 1. Identification of studies.[49]



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
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Results

Risk factors

Little is known about the global prevalence of LLV with rates ranging from 3% to 10%.[6] Recent studies indicated that 24%[8] to 38.7%[9] of study populations acquired LLV but their populations were considered to be lacking in resources in comparison to other studies with lower rates.[6,10] LLV is becoming increasingly prevalent with better testing methods, such as more specific viral load assays, yet there is little guidance on clinical management.[4,11,12] With definitions of LLV differing between studies and guidelines, it is difficult to properly assess true rates of LLV within any given population (Table 1).[4,11–13] It is unclear how many PLWH with LLV go on to develop virological failure (VF); however, a recent study revealed that the cumulative incidence rates were much higher in non-virally suppressed PLWH as well as with high LLV (200–400 copies/mL) with increased duration of LLV.[14] Another study reported that 38.2% of PLWH who experience LLV go on to develop VF.[15] The risk of developing LLV may be multifactorial but there are some noticeable risk factors that have been identified in studies aiming to answer the question of what leads to LLV and what are indicators of subsequent VF.[8,9,13,15–17] If healthcare providers can identify these risk factors, it can lead to being able to predict and manage LLV and, ultimately, prevent VF.

Of the 52 articles found using the search terms "HIV", "low-level viremia" and "risk factors" with a filter for articles published between 2014 and 2021, 7 were assessed (Table 2).[8,9,14,16–23] Factors associated with LLV included $CD4^+$ baseline nadir counts (<200 cells/mm^3),[8,9,17,24] baseline viral loads of >1,000,000 copies/mL,[8,9,17,24] non-adherence,[8] non-nucleoside reverse transcriptase inhibitor (NNRTI) use[8,17] and shorter duration of VS prior to ART switch from protease inhibitor (PI) to integrase strand transfer inhibitor (INSTI).[16] Furthermore, other factors associated with LLV leading to subsequent VF were LLV coupled with a high-level viraemic spike of >1000 copies/mL,[9,24] PI use compared to NNRTI,[18] ART experience[18] and restarting therapy at the start of the study, age <50 years,[18] Black race,[17,18] and male sex.[18]

Various studies reported that increased levels of LLV[10,14,17] with or without mention of duration were risk factors for VF, whilst others found that longer durations of LLV[9,17] with or without high levels of LLV (>200 copies/mL) were also risk factors. LLV and VF risk factors were also assessed in another study conducted by Qin et al.[14] that associated high LLV (>200 copies/mL) and non-suppressed viral loads with a higher rate of VF[10,14] than those who were virally suppressed. Additional factors considered high risk in developing LLV leading to VF included heterosexual acquisition of HIV, ART modification, use of co-trimoxazole during ART, and single or divorced patients.[14] Overall, PLWH who were MSM were diagnosed sooner, initiated medical care and ART sooner, were retained in care, and experienced ART modification or switches less often, reducing their risk of developing LLV and, subsequently, VF. As noted by the authors, this may be due to the overall growing acceptance, resources and support of the MSM community and HIV.[14] Changes to ART, including switches to second-line and third-line regimens, may be a factor but different therapy switches showed different levels of VF. It was found that, after 6 months of the new therapy, if the modification was appropriate and necessary as determined by toxicity, VF or for simplification, there was a reduced risk of VF. For PLWH with unnecessary ART switches, changes in therapy led to the possibility of drug resistance especially in switches to third-line agents. This study mentioned maintaining strict ART adherence and the need for proper follow-up after ART switch.[14]

Another study assessed ART switches from a PI-based regimen to a dolutegravir-based regimen and found that LLV and VLLV development was not significantly different between the two groups but the duration of VS prior to switching or continuation of PI regimen was a factor in the development of LLV or VLLV.[16] LLV and VLLV were not associated with VF, and those that did not achieve VS were often suboptimally adherent. This study concluded that switching patients to dolutegravir-based ART after VF on a PI regimen did not increase the risk of LLV or VLLV but shorter VS duration was associated with LLV or VLLV. A Chinese retrospective cohort study aimed to determine risk factors for high-risk LLV and its implications on VF incidence. This study concluded that high LLV (HIV-RNA >400 copies/mL) and the duration of LLV were associated with a higher risk of VF but medium LLV (200–400 copies/mL) and low LLV (50–199 copies/mL) were not.[9]

Of 18 resulting studies found with search terms including "LLV", "adherence" and "HIV", 7 were included (Table 2).[8,9,14,16–23] As expected, various studies consistently concluded that non-adherence was a determinant of LLV and is very probable to be a predictor of future VF.[8,17,19,22,23] Many of these studies also concluded other factors that contribute to LLV, including but not limited to drug resistance and higher baseline viral loads and $CD4^+$ cell counts, similar to risk factors identified previously.[8,19,22,23] One study concluded that good adherence may not be significant for achieving viral re-suppression but it is significant for preventing viral non-suppression and virological rebound.[20] Furthermore, patients who participated in drug holidays (defined as a >10% difference between overall adherence rate *versus* 60-day refills calculated adherence rates) *versus* patients with persistent non-adherence were more likely to develop LLV. They also concluded that patients with >95% adherence still have detectable HIV-RNA loads, which supports the latent HIV reservoir hypothesis where the virus continuously outputs HIV from infected cells.[21] Unsurprisingly, this study concluded that poor adherence was indeed associated with a higher incidence of LLV.[21] For patients who experienced intermittent LLV, these individuals required more frequent healthcare follow-up visits, which in turn resulted in greater adherence and less likelihood of developing VF.[17]

Table 1. Definitions.[4,11–13]

	JAMA/IAS[4]	HIVinfo.gov/DHHS[12]	EACS[11]	WHO[13]
Virological failure	Two consecutive VL measurements of HIV-RNA level of >200 copies/mL	Inability to maintain HIV-RNA VL measurement levels of <200 copies/mL	HIV-RNA VL of >200 copies/ mL after 6 months of ART	Two consecutive detectable VL of >1000 copies/mL measurements within a 3-month interval, after being on ART for at least 6 months
LLV	VL 50–200 HIV-RNA copies/mL, can be further defined as intermittent or persistent LLV	HIV RNA levels of <200 copies/mL	Not defined	HIV-RNA VL measurements of 50–1000 copies/mL
Viral rebound	Not defined	HIV RNA levels of ≥200 copies/mL, after VS	HIV-RNA VL of >50 copies/mL with formerly undetectable VL	Not defined
Viral blip	An outlier increase in HIV RNA levels to <1000 copies/mL that returns to undetectable levels	Isolated VL that is transiently detectable after VS, followed by a return to VS	Not defined	Isolated HIV-RNA VL measurements of 50–1000 copies/mL with a return to suppressed levels

ART, antiretroviral therapy; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; IAS, International AIDS Society; JAMA, Journal of the American Medical Association; LLV, low-level viraemia; VL, viral load; WHO, World Health Organization.

Table 2. Risk factors.[8,9,14,16–23]

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Zhang, T, 2020[9]	16-year retrospective cohort on 2155 PLWH	Shenyang, NE China 2002–2018	Inclusion: PLWH receiving first-line ART in China (two NRTIs and one NNRTI) VL controlled to <50 copies/mL after 6 months of ART Exclusion: VL data were incomplete	LLV definition: 50–1000 copies/mL (WHO definition of LLV) Medium LLV: 200–400 copies/mL Low LLV: 50–199 copies/mL	Median baseline VL measurement was 4.5 $\log_{10}$ HIV-RNA copies/mL, median follow-up time was 3.4 years, majority were male sex, median age at diagnosis 37 years, 79.2% homosexual infection, ART most commonly used was TDF+3TC+EFV	Risk factors for VF included any level of LLV coupled with a high-level blip of >1000 copies/mL (p<0.01) and an increased duration of LLV (>3 months, HR 3–6 months: 6.2, 6–12 months: 9.74, >12 months: 7.52) (p<0.01)

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Zhang, T, 2020[9] (*Cont.*)					38.7% experienced at least one episode of LLV VF increased with increasing levels of LLV and duration of viraemia 72.1% of the reported cases of LLV were considered blips and only 5.1% of LLV persisted for more than 12 months Least favourable outcomes in those with >400 copies/mL and LLV duration of >12 months Risk of VF increased with HLLV for any duration or any level LLV coupled with high-level blip; MLLV or LLLV were not associated with VF	Factors that were associated with high-risk LLV included $CD4^+$ baseline nadir counts <200 cells/mm^3 (p=0.011), baseline VL >1,000,000 copies/mL (p=0.006), ART >60 months or didanosine-based drug regimen (p=0.004) and subtype B infection (p=0.001)
Qin, S, 2021[14]	Retrospective follow-up on 1860 PLWH	Guangxi, China 2003–2019	Inclusion: Available baseline VL data before ART initiation ART for at least 6 months Two or more VL records during follow-up Interval between VL test not more than 12 months Exclusion: Not matching inclusion criteria	VF defined as VL >400 copies/mL High LLV defined as 201–400 copies/mL Low LLV defined as 20–200 copies/mL	VL >200 copies/mL after 6 months of ART were high risk for VF Demographics of high-risk group: male sex and married or cohabitating, median age of diagnosis 39 years, median age of ART initiation 40 years Risks factors for high-risk group: single or widowed, ART modification, acquired HIV heterosexually, cotrimoxazole for opportunistic infection prophylactic use (p<0.001)	Risk factors for VF included high LLV (>200 copies/mL) (p<0.001) and non-suppressed viral levels (p<0.001) Risk factors that were associated with LLV: heterosexual acquisition, ART modification, use of co-trimoxazole during ART (p<0.001) and single or divorced patients High LLV also had the highest cumulative incidence rate for AIDS-related death (p<0.001)

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Gaifer, Z, 2020[8]	Prospective cohort with 153 PLWH	Oman, 2020	Inclusion: PLWH 18 years and older who were taking ART for more than 12 months and had at least 2 HIV RNA measurements 1 year after ART initiation Exclusion: PLWH not taking ART Death, lost to follow-up or discontinuation of ART within the first year	LLV defined as two consecutive HIV RNA VL measurements of 50–200 copies/mL after 12 months of ART therapy VF defined as inability to virally suppress HIV RNA levels to <200 copies/mL by 1 year of ART Secondary VF was defined as the inability to achieve or maintain VS to <200 copies/mL after initial VS of <50 copies/mL	Median duration of follow-up was 48 months, mean age: 44 years, mean sex: male, median duration of HIV infection was 7 years, pretreatment CD4 was 171 cells/mm^3, and ART used was 2 NNRTI + PI or NNRTI, most common backbone being Tenofovir + Emtricitabine 104/150 patients enrolled claimed adherence to their ART regimen; after 12 months of ART, 60 (40%) patients had achieved VS, 37 (24%) had LLV and 53 (35%) patients had VF Secondary subsequent VF incidence was 3 and 7 cases per 1000 patient-months for VS and LLV, respectively Older age (p=0.009), longer HIV infection duration (p=0.0001), higher pretreatment HIV RNA and lower CD4 cell count (p=0.0269), ART adherence (p=0.027), and NNRTI (p=0.023) were found to be associated with secondary VF	LLV PLWH are at higher risk for VF and should be monitored more closely. LLV has a higher risk of VF (p=0.02) Age, duration of HIV infection, pretreatment HIV RNA, pretreatment CD4 cell counts, adherence, and NNRTI use were associated with secondary subsequent VF in this study
Chen, GJ, 2021[16]	Single-centre retrospective observational cohort with 492 PLWH included		Inclusion: PLWH 20 years and older and received HIV care at NTUH	LLV was defined as VL between 50 and 999 copies/mL and events between 20 and 50 copies/mL were defined as VLLV	PI-based regimen was used initially, PLWH who switched regimens were given a dolutegravir-based regimen	Switching to dolutegravir-based therapy does not increase the risk of VLLV or LLV

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Chen, GJ, 2021[16] (*Cont.*)		National Taiwan University Hospital (NTUH) between September 1, 2016, and April 20, 2017	Previous VF or intolerance to first-line NNRTI-based therapy who received boosted or unboosted PI regimens with VL <200 copies/mL for more than 6 months Exclusion: Previous treatment failure to INSTIs and PLWH with emergent genotypic resistance to dolutegravir		Risks of developing VLLV or LLV were similar between groups in PLWH who were virally suppressed; PLWH who experienced VF, suboptimal adherence was reported VLLV or LLV was not found to be associated with VF Shorter duration of VS is a risk factor for VLLV or LLV after switch	No difference in risk of developing LLV in PI-based and Dolutegravir-based groups Shorter duration of VS was identified as a risk factor
Joya, C, 2019[17]	NHS prospective, multicentre, open cohort with PLWH who were Department of Defense beneficiaries, 2006 PLWH were included, this analysis was a retrospective analysis	The United States, 1996–2017	Inclusion: ART initiation during the study period that had at least two documented VL 6 months after initiation whilst on ART Exclusion: Those not meeting the inclusion criteria	LLV was defined as 50–199 copies/mL, high LLV was a VL of 200–1000 copies/mL LLV was subcategorized into intermittent LLV and persistent LLV Continuously suppressed was defined as VL <50 copies/mL	Median age 29.2 years, 93% men, racially diverse, median CD4 count was 454 cells/μL, NNRTI-based ART regimen was most common Risk factors found to be associated with VF were high LV and persistent LLV, ARV prior to ART, Black ethnicity ($p<0.001$) higher VL at ART initiation ($p<0.008$) Older age at ART initiation and NNRTI or INSTI use were found to be protective factors Persistent LLV is clinically significant and should be addressed	Risk factors for VF in this study were Black race ($p=0.02$), diagnosed with HIV before the year 2000 ($p<0.0001$), longer median duration from diagnosis to ART initiation, a lower $CD4^+$ nadir ($p<0.0001$), treated with mono or dual ARV prior to ART initiation ($p<0.0001$), initiated an ART regimen with unboosted PI ($p<0.0001$), participants with high LV (200–1000 copies/mL) and persistent LLV (50–199 copies/mL on more than 25% of measurements)

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Joya, C, 2019[17] (*Cont.*)				VF was defined as 200 copies/ mL or more on two consecutive measurements or any VL of >1000 copies/mL 6 months after initiation of ART whilst on ART		Patients with intermittent LLV (50–199 copies/mL on less than 25% of measurements) were more likely to be White, older at ART initiation, initiated ART with NNRTI, less likely to have performed ARV with mono or dual therapy prior to ART initiation, have a lower CD4 nadir and count at initiation and had higher VL at ART initiation; concludes that patients with intermittent LLV required more frequent healthcare follow-ups, which in turn resulted in greater adherence to ART; intermittent LLV, older age at ART initiation, and use of NNRTI or INSTI were found to have a protective effect against VF
Fleming, J, 2019[18]	Cohort study with 2795 PLWH	The United States from January 1, 2005, to December 31, 2015	Inclusion: Started ART prior to end date of study period No prior history of ART or, if ART history, new regimen was started at least 90 days after enrolment and no VS at enrolment HIV RNA of >200 copies/ mL at ART initiation (assays used had a lower limit of 50 copies/mL of detection)	VF was defined as two consecutive VLs of >500 copies/ mL, and LLV was further categorized into two categories as two consecutive VLs between 51–200 copies/mL and 201–500 copies/mL	LLV in both 51–200 and 201–500 copies/mL categories were associated with VF whilst blips in PLWH within each group were not Viral blips were not associated with VF Sensitivity analysis showed that ART-naïve PLWH with blips in higher LLV groups may benefit from close monitoring because of a higher risk associated with VF	Risk factors for VF include PI use compared to NNRTI, ART-experienced at baseline, Black race, age younger than 50 years and male sex

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Fleming, J, 2019[18] (*Cont.*)			At least two consecutive VS HIV RNA levels after initiation Exclusion: Not meeting inclusion criteria		Inverse association in a number of VL measurements taken and VF; adherence was not assessed but the inverse relationship of increased lab measurements taken was theorized to be because of an increased patient–practitioner relationship and interaction Other factors that were associated with increased VF were PI use compared to NNRTI, ART-experienced at baseline, male sex, Black race and ages younger than 50 years	
Inzaule, SC, 2020[20]	Multicountry adult cohort study with 2737 PLWH	Sub-Saharan Africa, 2007–2014	Inclusion: HIV infected adults age 18+ Received first-line therapy with an NNRTI and two NRTIs Had a genotype resistance test available Viral load test available at 1 and/or 2 years Exclusion: Those not meeting the inclusion criteria	VL measurements at months 12 and 24 of ART were either: - viraemic episode (≥1000 cps/mL) - VS (<1000 cps/mL) - LLV (50–999 cps/mL)	Measured viraemic episodes at 12 and 24 months Non-adherence to medications may account for 30% of viral non-suppression [173/1935 (8.9%)] Viral non-suppression was found to be due to pretreatment HIV drug resistance to NNRTIs in 10%; however, drug resistance was only attributable to 1.1% virological rebound episodes, compared to non-adherence (14%) and LLV (29%)	Study concludes that non-adherence accounts for only a small percentage of non-achieved viral resuppression (2.4%) compared to acquired drug resistance (34%)

(Continued)

Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Goupil de Bouillé, J, 2019[19]	Multicentre, case–control, epidemiological study with 43 PLWH	France, 2013–2015	Inclusion: Patients with at least two VLs between 50 and 500 copies/mL Exclusion: No ART delivery at designated pharmacy Partial or missing pharmacy data Follow-up <12 months	LLV was defined as ≥2 VL of 50–500 copies/mL	After 12 months, 13 patients had therapeutic success, 9 had VF and 15 had LLV Those 15 were matched to 45 control (virologically suppressed) patients, matched by age and sex; split into two groups, >80% adherent and <80% adherent Assessed adherence based on pharmacy profile information	LLV group had significantly lower adherence scores (53.3% <80% $p<0.01$) *versus* control group with VS (6.67% <80%) Conclusion of this study is that adherence should remain a first-line management strategy for treating LLV
Maggiolo, F, 2017[21]	Single centre, cohort study with 2789 PLWH	Italy, 2017	Inclusion: All HIV-positive patients that had received at least 1 day of ART Exclusion: Those not meeting the inclusion criteria	None	Primary outcome was adherence to cART, measured by pharmacy refill records Calculations were completed to assess for the presence of drug holidays (episodic non-adherence) Adherence was classified as >95% or <95% Mean cART duration of 8.9 years ($p=0.001$); 2.2 years on current ART regimen ($p=0.003$) Three drug regimens were most common, consisting of NRTIs, NNRTIs and PIs	Concludes patients who participate in drug holidays are more likely to experience viral blips than patients with consistent non-adherence Concludes that detectable HIV-RNA levels can be seen in patients with >95% adherence, supporting the latent HIV reservoir hypothesis Concludes that VS can be achieved via moderate cART adherence; however, poor adherence is associated with LLV

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Table 2. (*Continued*)

Study Authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Bernal, E, 2018[22]	Open, multicentre, prospective cohort study with 5986 PLWH	Spain, 2004–2015	Inclusion: HIV-positive, naive patients who initiated ART and remained on it for 6 months 18 years and older Achieved VS (<50 copies/mL) within 3–9 months of initiation Exclusion: Those not meeting the inclusion criteria	LLV50–199 is defined as 50–199 copies/mL x 2 VL in 1 month LLV200–499 is defined as VL 50–499 x 2 VL in 1 month with 1 VL being between 200 and 499 copies/mL	Non-consecutive blips were not included Median age of 36 years, 83% male sex, 294 cells/mL average CD4 cell count at ART initiation, and over half of the patients started with an NNRTI-based regimen Median time between ART initiation and LLV 50–199 copies/mL and 200–499 copies/mL was 1.3 years and 2.3 years, respectively	LLV was found to be more likely in patients with a baseline VL of >100,000 copies/mL, those started with a 2 NRTI + PI regimen, and patients with hepatitis C antibodies Lower rates of LLV were seen in patients enrolled in 2012–2015 compared to those enrolled in 2008–2011, possibly due to better adherence from single-tablet and well-tolerated regimens emerging VF observed at 5 years after VS was most common in the LLV200–499 group ($p<0.001$)
Taramasso, L, 2020[23]	Retrospective cohort study with 1607 PLWH	Italy, 2015–2017	Inclusion: HIV-positive patients, 18 years and older with at least one HIV-RNA measurement Exclusion: Those not meeting the inclusion criteria	LLV was defined as HIV-RNA VL 50–500 copies/mL for 4 consecutive months after achieving VS on ART; VF was defined as VL >1000 copies/mL and VS as undetectable values for 6 consecutive months after LLV event	Of all patients enrolled, only 21 patients presented with LLV Only 9/21 (43%) patients reported having good adherence to their ART regimen; adherence counselling was reinforced and adherence measures were determined by self-report or through pharmacy records	For causes of persistent LLV, the study concluded that poor adherence was responsible for 38%, followed by resistance (33%) and unknown (29%)

3TC, lamivudine; ART, antiretroviral therapy; ARV, antiretroviral; cART, combined antiretroviral therapy; EFV, efavirenz; HLLV, high low-level viraemia; INSTI, integrase strand transfer inhibitor; LLLV, low low-level viraemia; LLV, low-level viraemia; MLLV, medium low-level viraemia; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PLWH, people living with HIV; TDF, tenofovir disoproxil fumarate; VL, viral load; VLLV, very low-level viraemia; VF, virological failure; VS, virological suppression; WHO, World Health Organization.

Genotyping

Of the 15 articles identified in PubMed with search terms "HIV-1" AND "genotype* AND "low-level viremia" with a filter for articles published between 2014 and 2021, 3 were included (Table 3).[23–25] HIV-1 genotyping proviral DNA resistance testing (GRT) with or without the use of historic RNA viral resistance testing has been an option to help guide clinical decision-making in situations of LLV and can be used where first-line ART has not been effective in achieving VS.[6] In one study, it was found that 86% of PLWH with LLV had a resistance mutation.[23] Clinicians can also use historic RNA GRT, also known as archived RNA GRT, to guide treatment regimens. According to some guidelines, HIV RNA GRT may not be a reliable option for PLWH with LLV due to the possibility of results being inaccurate with HIV RNA <500 copies/mL[12] or <1000 copies/mL.[24] Current European AIDS Clinical Society guidelines recommend HIV-1 RNA GRT for levels within 200–500 copies/mL and in specialized facilities for levels below 200 copies/mL.[11] Whilst Department of Health and Human Services guidelines suggest GRT in viral levels above 1000 copies/mL and warn that GRT taken within 500–1000 copies/mL may be unsuccessful.[12]

One study assessed the feasibility and reproducibility of HIV-1 RNA GRT in patients with LLV and VLLV.[25] This study aimed to determine the overall success rate of RNA GRT in levels below 500 copies/mL as LLV and VLLV have an increased need for GRT testing. The results obtained from this study suggest that patients with VLLV and LLV can obtain GRT results with a high rate of success (Table 3).[24] This can be used as an aid in clinical practice for those patients with even the lowest levels of viraemia.

A different study aimed to determine if proviral DNA GRT testing was a safe and reliable option for changing therapy in PLWH with LLV in comparison to continuation of the current ART regimen.[24] ART therapy changes made with the use of proviral DNA GRT lead to successful VS with levels of <20 copies/mL within 6 months in 54% of PLWH, but maintaining the same regimen led to successful VS with levels of <20 copies/mL within 6 months in 74% of patients.[24] Based on the results of the study, GRT-guided change was deemed safe based on the results for both therapy-guided change and the decision to maintain the same therapy.[24] This study also found that there was a correlation between historic RNA GRT and proviral DNA GRT but DNA GRT did not detect all the mutations that were present over time and was better at detecting newly formed resistance (33% *versus* 24%) whilst RNA GRT detected prior resistances better (34% *versus* 45%).[24] There was an added benefit to using both DNA and RNA GRT, as mutations not found in one were found in the other; thus, the use of both techniques, if available, would be a better option than either alone. In the absence of RNA GRT, DNA GRT can be used safely. An interesting find was that PLWH who had achieved VS benefit from DNA GRT to guide therapy switch with a lower rate of VF in those who went through an ART switch in comparison to those who maintained the same regimen (5% *versus* 19%).[24] In addition, adherence was assessed in this study as being a contributing factor to VF. Overall, the use of proviral DNA GRT was safe in guided therapy changes with or without the use of RNA GRT, and proviral DNA GRT is a safe alternative especially in cases where there is no historic RNA.

In PLWH who are ART naive who are to be started on NNRTIs, nucleoside reverse transcriptase inhibitor (NRTIs) or PIs, it is recommended to obtain a baseline reverse-transcriptase prodrug genotypic resistance test before starting those ART regimens.[4] Currently, it is not recommended to obtain a proviral GRT prior to starting INSTI ART due to low rates of INSTI resistance (11% for INSTIs, 52% for NRTI, 57% for NNRTI, 26% for PI).[26] It is recommended to test INSTI resistance with proviral GRT if transmission of INSTI is suspected in a patient who may have obtained HIV from a partner who has documented or suspected INSTI resistance. Once PLWH have been on ART for 4–6 weeks and HIV RNA levels have not decreased significantly despite confirmed medication adherence, it is recommended to obtain GRT.[4] In patients with previous VS who have two consecutive HIV RNA viraemia measurements with levels above 200 copies/mL, GRT should be performed.[4] If GRT is unsuccessful, a proviral HIV DNA test should be performed. Changing regimens in patients with intermittent or persistent LLV is not recommended, and other causes of failure should be assessed. Changing ART is only recommended in cases where toxicity or tolerability is an issue.

According to current guidelines,[11,12] genotypic testing is recommended prior to ART initiation, if not previously tested, and ideally at the time of HIV diagnosis. In a situation where ART should be started immediately without the results of the genotypic test being available, initial ART with a high barrier to resistance should be selected. In situations of treatment modification, cumulative GRT should be evaluated prior to switching ART as well as a complete antiretroviral (ARV) history with HIV viral load (HIV-VL), tolerability issues and phases of viraemia with other ARV therapies. Proviral DNA resistance testing may be useful in patients with unavailable GRT history, multiple VFs or LLV at time of ART switch. Proviral DNA resistance testing is not currently recommended due to its inability to detect prior resistance mutations and the fact that it may detect clinically irrelevant resistance.

Based on these studies[23–25] and current guidelines,[4,11,12] it is plausible to use both historical RNA GRT and current proviral DNA GRT in patients with LLV. It is a safe option and there is a correlation between the two test methods that can help guide clinical decision-making. The benefit of using historical RNA GRT over proviral DNA GRT is the ability of historic RNA GRT to identify archived mutations; however, using the two synchronously can be beneficial and safe.

Viral blips

The association between viral blips, LLV and VF has been questioned in various studies.[18,27–30] Of the 18 articles found in PubMed with the search terms "viral blips" AND "low-level viremia" with a filter for articles published between 2014 and

Table 3. Genotyping.[23–25]

Study authors	Study design	Location/time frame	Pertinent inclusion/ exclusion criteria	Results	Conclusion
Bruzzone, B, 2014[25]	In vitro studies analysis with 168 samples	Italy, January 2013 to December 2014	Inclusion: HIV RNA <1000 copies/mL Exclusion: Not meeting inclusion criteria	Success rates per HIV RNA level: • 82.1%, <50 copies/mL • 85.3%, 50–100 copies/mL • 94.4%, 101–200 copies/mL • 100%, 201–1000 copies/mL	HIV RNA GRT can effectively be performed in levels under 500 copies/mL in LLV and VLLV PLWH
Meybeck, A, 2020[24]	Retrospective cohort with 304 PLWH	France, January 2012 to December 2017	Inclusion: All not meeting exclusion Exclusion: PLWH involved in a clinical trial VL >200 copies/mL	• ART change appeared to be safe with use of DNA GRT and historical RNA GRT • Factors independently associated with VF: high levels of HIV DNA, low nadir CD4, shorter duration of VS (<20 copies/mL) • DNA GRT can be used in absence of historical RNA GRT	DNA GRT can be a useful tool in choosing ART for both PLWH who are VS or have LLV in addition to previously attained resistance tests and history of resistance
Taramasso, L, 2020[23]	Retrospective cohort with 1607 enrolled	Italy, 2015–2017	Inclusion: • >18 years old • Performed at least one HIV-RNA at Policlinico San Martino Hospital Exclusion: • Not meeting inclusion criteria	• Median age 50 years, men 76%, HIV VL prior to ART initiation 316,227 copies/mL, CD4 nadir prior to initiation 238 cells/mm^3 • Therapy used was 19% NNRTIs, 33.3% PIs, 23.8% INSTIs, 23.8% INSTI + PI • GRT was performed in 52% of the patients with 86% of those patients having found a resistance mutation • GRT-guided therapy leads to 83% VS	Adherence and GRT should be considered in trying to reduce LLV

ART, antiretroviral therapy; GRT, genotypic resistance testing; INSTI, integrase strand inhibitors; LLV, low-level viraemia; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; PLWH, people living with HIV; VF, virological failure; VL, viral load; VLLV, very-low-level viraemia; VS, viral suppression.

2021, 4 were assessed (Tables 2 and 4).[18,29,31,32] One study evaluated VF after a blip in PLWH and the association of blips between 51 and 200 copies/mL compared to between 201 and 500 copies/mL.[18] In this study, viral blips were defined as an isolated viral load between 51 and 500 copies/mL after attainment of VS. This study concluded that viral blips were unlikely to be associated with VF in both high and low LLV groups. Prior studies have also shown consistent results to this study,[27,32] whilst other studies mentioned that blips may contribute but are not the only factor leading to VF.[31,33]

The 2020 *JAMA* guidelines do not recommend switching ART based on a viral blip. Conversely, they recommended a review of potential causes for blip occurrence, including socioeconomic environment, adherence and drug interactions.[4] The results found in this study were consistent with current guidelines recommending no ART modification if a blip occurs and that this should only be monitored. Viral blips were not addressed in European AIDS Clinical Society (EACS) guidelines.[11] A sensitivity analysis showed a possible association of VF in PLWH who were ART naive and who were in the high LLV group, leading researchers to believe that there may be an added benefit to monitoring these patients more carefully. Another study showed viral blip occurrence in PLWH with PI-based regimens in comparison to those on NNRTI-based regimens but a notable limitation was the lack of evaluation of INSTI-based regimens.[31] An interesting finding in another study was that residual viraemia (detectable viral load of <50 copies/mL) in the year prior to a first viral load of >50 copies/mL was found in PLWH before the development of a viral blip or LLV.[29] This study concluded that LLV and blips were associated with residual viraemia and that these PLWH were at higher risk for VF.

ART modification

Of 39 studies retrieved using the search terms "LLV", "intensification" and "HIV" from 2014 to present, 7 were included (Table 5).[5,14,16,17,23,34,35] A Taiwanese retrospective cohort study aimed to evaluate the effect of a dolutegravir *versus* PI regimen in PLWH as well as its effects on the incidence of LLV and VF. The study concluded that neither LLV/VLLV nor the third agent (dolutegravir *versus* PI) had significant effects on future VF.[16] A prospective cohort study performed in the United States investigated the effect of persistent LLV on subsequent VF and found that intermittent LLV was actually protective against the development of VF; however, unboosted PI regimens and prior mono or dual ARV use were risk factors for VF.[17] Another study evaluated baseline demographic and clinical characteristics of patients who present with persistent LLV as well as the clinical management strategies employed. The authors concluded that, in patients with inadequate ART due to genotype resistance, poor adherence or drug–drug interactions, intensification of an ARV regimen resulted in increased VS rates.[23] A retrospective cohort study performed in China investigated high-risk viral load events and their association with VF and concluded that ART modification is a viral load high-risk factor for VF.[12] Another randomized controlled trial assessed the effect of switching ART regimens in patients with LLV and whether or not it was beneficial. The study concluded that switching from first-line NNRTI-based ART to second-line ART in patients with persistent LLV (100–999 copies/mL) resulted in increased VS and these patients were also more likely to achieve VS by week 24 instead of 36.[34] A Swedish observational cohort study inquired on the effects of LLV on all-cause mortality, serious non-AIDS events and AIDS. The study concluded that patients with LLV (50–999 copies/mL) were at increased risk of all-cause mortality and patients with LLV (200–999 copies/mL) were also at increased risk of serious non-AIDS events. They also deduced that patients with VS were less likely to be started on a PI regimen and that adjusting the ART regimen did not change the increased all-cause mortality risk in patients with LLV.[5] A proof-of-concept study conducted in Spain investigated patients on the original ARV regimen of ritonavir-boosted PIs being intensified with raltegravir 400 mg twice daily for 24 weeks and discovered lower intermediate residual viraemia levels with raltegravir intensification.[35] In summary, 4 out of 5 studies (2 studies did not provide analysis on this) concluded that LLV, although in varying levels within 50–999 copies/mL, increased the risk of subsequent VF, with Chen et al. being the outlier.[5,8,14,17,34] A higher baseline viral load and lower baseline $CD4^+$ T cell counts were risk factors for developing LLV and VF.[5,8,17] In summary, intensifying or modifying ART resulted in decreased VF rates and increased VS in patients with LLV in 4 studies.[16,23,34,35] Intensifying or modifying ART regimens resulted in no change in all-cause mortality risk associated with LLV in 1 study.[5] Interestingly, 1 study found that modifying ART regimens was a high-risk factor for VF.[14]

Discussion

Despite advances in the treatment of HIV, the management of LLV lacks standardization. One notable limitation of the currently available literature is the use of different definitions of LLV. Furthermore, some studies classified LLV into different subcategories. Using different classifications for the same term can make it increasingly difficult for practitioners to appropriately assess and interpret results from one study and apply it to clinical practice. Furthermore, different terms are used to define the same range; for example, VF in one study was defined as a viral load of >400 copies/mL[14] whilst another study that used the WHO definition of LLV defined it as a viral load of 50–1000 copies/mL.[9] Developing universal terminology to define LLV and VF would assist in developing and adopting standardized treatment recommendations for the management of LLV to prevent VF.

Addressing and being aware of risk factors can assist healthcare providers in preventing LLV and, subsequently, VF. Between the studies that were assessed, common risk factors associated with LLV and VF were longer duration of HIV infection, shorter duration of VS prior to ART switch, higher viral load in those

Table 4. Viral blips.[29,31,32]

Study authors	Study design	Location/ time frame	Pertinent inclusion/exclusion criteria	Results	Conclusion
Sörstedt, E, 2016[31]	Retrospective study with 735 PLWH enrolled	Sweden, August 2007 to December 2013	Inclusion: • ART-naive PLWH • ART initiation between 2007 and 2013 Exclusion: • PLWH not suppressed after 6 months of ART	• Viral blips were found in 10.3% of PLWH and 2% of samples • Median blip VL was 76 copies/mL, follow-up time was 170 weeks • Baseline VL was higher in PLWH with viral blips (p=0.007)	There is an association with blips and higher baseline VLs that leads to an increased risk of VF
Crowell, TA, 2020[32]	Prospective cohort study with 326 PLWH	Thailand, May 2009 to May 2017	Inclusion: • Initiation of ART with confirmed HIV RNA <20 copies/mL • Continued ART for at least 1 year Exclusion: • Not meeting inclusion criteria	• Viral blips had low magnitude after ART initiation • Blips were of low frequency in those on ART • Early ART initiation reduced frequency of blips • Viral blips were more common in PLWH who had lower CD4 counts median (308 *versus* 379 cells/mm^3; p=0.018) and higher HIV RNA (6.6 *versus* 5.8 $\log_{10}$ copies/mL; p<0.001)	In PLWH with chronic infection, initial VL at the initiation of ART was a strong predictor of blips
Hofstra, LM, 2014[29]	93 PLWH from Observational AIDS Therapy Evaluation in the Netherlands cohort	Netherlands, April 2009 to August 2010	Inclusion: • Adult PLWH with first detectable VL during study period • ART therapy for more than 1 year who had at least two consecutive readings of <50 copies/mL Excluded: • Documented treatment interruptions	• Shorter ART and PI-based regimen were found in patients who had LLV as opposed to blips • 50% of PLWH had a positive residual viraemia level in the year preceding LLV as opposed to 3% in the VS group (p<0.001)	• Residual viraemia in PLWH the year preceding the first measurement of >50 copies/mL was associated with development of LLV or viral blip (OR 10.9, 95% CI 2.9–40.6) • LLV PLWH were at higher risk for VF, as viral blips had a much lower risk

ART, antiretroviral therapy; LLV, low-level viraemia; PI, protease inhibitor; PLWH, people living with HIV; VF, virological failure; VL, viral load; VS, virological suppression.

Table 5. ART modification.[5,14,16,17,23,34,35]

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Amstutz, A, 2020[34]	Multicentre, parallel-group, open-label superiority randomized controlled trial with 80 PLWH	Southern Africa, 2017–2019	Inclusion: HIV-positive patients taking NNRTI-based first-line ART for at least 6 months Patients presented 2 VL measurements ≥100 copies/mL and one being between 100 and 999 copies/mL Exclusion: Poor adherence defined as missing at least 1 dose per month WHO stage 3 or 4 clinical conditions at enrolment On a PI at enrolment	VS defined as VL <50 copies/mL at 36 weeks after randomization was the primary endpoint	Enrolled participants had a median age of 42 years, median baseline VL of 347 copies/mL and a median ART duration of 5.9 years; there were 40 patients randomized to both the control and switch group; participants were followed up for 36 weeks Patients who were in the switch group were switched from an NNRTI to a PI and one of the two NRTIs was also switched to one that the patient had not been on previously; lamivudine was kept for all patients; all patients had only been exposed to NRTIs and NNRTIs, the most common ART regimen was tenofovir disoproxil fumarate/lamivudine/efavirenz Patients who were in the control group stayed on standard of care, first-line NNRTI-based ART 56 (70%) patients had VLs between 100 and 599 copies/mL whilst 24 (30%) patients had VLs between 600 and 999 copies/mL; 22/40 (55%) in the switch group and 10/40 (25%) in the control group achieved VS (p=0.009); post hoc analysis concluded that, of the 55 patients that had VL 200–999 copies/mL, 54% in the switch group and 17% in the control group achieved VS	After 36 weeks, more patients in the switch group compared to the control group were able to achieve VL <20 (p=0.002), VL <100 (p=0.05), VL <200 (p=0.003), VL <400 (p=0.02) and VL <600 (p=0.04) but not VL <1000 copies/mL Sustained VF was seen in 30% and 70% in the switch and placebo groups, respectively (p=0.001) The study concluded that switching from first-line NNRTI-based ART to second-line ART regimens in patients with persistent LLV (100–999 copies/mL) resulted in increased VS and these patients were also more likely to achieve VS by week 24 instead of 36

(Continued)

Table 5. (*Continued*)

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Amstutz, A, 2020[34] (*Cont.*)					No deaths, hospitalizations, or grade 3 or 4 WHO events were reported; however, adverse events were more commonly reported in patients in the switch group (p=0.002); self-reported good adherence was lower at 51% in the switch group *versus* 72% in the control group	
Elvstam, O, 2020[5]	Nationwide observational cohort study with 6956 PLWH	Sweden, 1996–2017	Inclusion: Started cART in January 1996 or later At least 15 years old at cART initiation Had a personal identity number. Had at least 2 VL measurements 6 months after starting cART Exclusion: Those not meeting the inclusion criteria	Cardiovascular diseases, venous thromboembolic disease, pulmonary arterial hypertension, chronic kidney disease, decompensated liver disease and non–AIDS-defining malignancies were all considered to be serious non-AIDS events Participants were categorized by their 6-month VL measurements to either 1) VS (<50 copies/mL) 2) LLV (50–999 copies/mL x 2 consecutively at least 1 month apart) 3) non-suppressed viraemia (>1000 copies/mL at least once)	Enrolled participants had a median follow-up time of 5.7 years and a median baseline VL of 73,000 copies/mL before ART initiation 58% of enrolled participants were on a cART regimen that included a PI, 36% included NNRTI, 20% included abacavir and only 8% included an INSTI At the end of the follow-up period, 60% of patients were VS, 5% LLV 50–199 copies/mL, 4% LLV 200–999 copies/mL and 31% non-suppressed viraemia Of the 5169 individuals who achieved VS, 35% had at least one isolated VL between 50 and 999 copies/mL Patients with LLV had statistically significant higher mortality, so long as >25% of the VL measurements were >50 copies/mL Older age, male sex, injection drug use and treatment interruptions were all also associated with higher all-cause mortality	Patients with VS were less likely to be started on a PI-based ART regimen, had lower rates of prior cART use and were more likely to be included in a later date of the study Adjusting the ART did not change the increased all-cause mortality risk in patients with LLV Neither PI, NNRTI, INSTI or abacavir were associated with any increased risk of all-cause mortality In conclusion, LLV 50–999 copies/mL was associated with increased all-cause mortality, and patients with LLV 200–999 copies/mL were also at higher risk for SNAEs

(Continued)

Table 5. (*Continued*)

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Taramasso, L, 2020[23]	Retrospective cohort study with 1607 PLWH	Italy, 2015–2017	Inclusion: HIV-positive patients, 18 years and older with at least one HIV-RNA measurement Exclusion: Those not meeting the inclusion criteria	LLV was defined as VL of 50–500 copies/ mL for 4 consecutive months after achieving VS on ART VF was defined as VL >1000 copies/mL and suppression as undetectable values for 6 consecutive months after LLV event	Out of all enrolled patients throughout the study period, 21 presented with persistent LLV 7/21 (33%) of patients presented with at least one prior episode of LLV and 15/21 (71%) presented with at least one episode of VF 12 patients reported non-adherence' of those, 3 patients had suboptimal ART and changes were made resulting in 3/3 (100%) VS; 9/12 patients had an optimal ART regimen; of those, 3 ART regimens were changed which resulted in 3/3 (100%) VS; 6/9 patients that did not change their ART regimens resulted in the first VF with only 4/6 achieving VF and 2/6 VF	7 patients with no evidence of suboptimal ART intensified their regimen, 6 patients achieved VS by adding an INSTI-based or PI-based therapy, 1 patient had persistent LLV even after switch 6 patients with reported good adherence had adequate, fully effective ART regimens; 4 patients' regimens were changed and 2 were left unchanged; no VF were reported; however, in patients whose regimens were changed, 75% achieved VS compared to only 50% in the unchanged arm
Puertas, MC, 2018[35]	Proof-of-concept, single-arm, pilot clinical trial with 33 PLWH	Spain, 2018	Inclusion: HIV-positive patients that had VS (<50 copies/ mL) on PI/r ART (400/100 mg lopinavir/ritonavir BID or 800/100 mg darunavir/ritonavir daily) for at least 1 year and had switched from triple ART to PI/r whilst in VS $CD4^+$ T cell count ≥500 cells/mm^3 No history of VF on PI-based therapy	*De novo* infection markers include long terminal repeats (2-LTR); 2-LTR circles in $CD4^+$ T cells are a surrogate marker of recent infection	Participants enrolled had a mean age of 47 years, median baseline VL of 5.2 log_{10} HIV-RNA copies/mL and had a median ART duration of 7.4 years All 33 patients (18 on darunavir/ ritonavir and 15 on lopinavir/ ritonavir) underwent the raltegravir intensification regimen that consisted of raltegravir 400 mg twice daily 97% of patients self-reported adherence levels >96%	PI/r intensification with raltegravir resulted in increased low-level viral replication but decreased the frequency of detectable intermediate residual viraemia (10–60 copies/mL) suggesting that dual therapy may result in improved VS

(Continued)

Table 5. (*Continued*)

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Puertas, MC, 2018[35] (*Cont.*)			Exclusion: Those not meeting the inclusion criteria		Isolated viral blips were seen in 4 patients with only 1 being noted in the intensification period but no VF was observed Higher amounts of residual viraemia samples between 10 and 60 copies/ mL were seen in the preintensification phase (21%) and decreased in the intensification phase (7%), and increased again in the withdrawal phase (15%) 2-LTR circles were found in 18 patients, the number detected transiently increased during the first 2 months of intensification but no significant changes were noted from overall beginning to end of intensification period	
Chen, GJ, 2021[16]	Single-centre retrospective observational cohort with 492 PLWH	NTUH, September 1, 2016 to April 20, 2017	Inclusion: PLWH 20 years and older and received HIV care at NTUH Previous VF or intolerance to first-line NNRTI-based therapy who received boosted or unboosted PI regimens with VL <200 copies/mL for more than 6 months	LLV was defined as VL between 50 and 999 copies/mL and events between 20 and 50 copies/mL were defined as VLLV The WHO definition of VF was used (>1000 copies/mL)	Enrolled participants had a median age of 40.2 years in the dolutegravir group and 44.7 years in the PI group and had a median baseline VL of 1.3 $\log_{10}$ HIV-RNA copies/mL; median observation was 49 weeks Treatment arm 1: PLWH were switched to 2 NRTIs and dolutegravir regimen (DTG group); treatment arm 2: PLWH continued their PI + 2 NRTIs regimen (PI group) Of the 492 patients, 183 switched to the DTG group whilst 309 patients continued in the PI group	Univariate analysis concluded that the choice of the third agent in the ART regimen (dolutegravir or PI), as well as LLV or VLLV events, was significantly associated with VF Patients who were virologically suppressed for shorter amounts of time were at higher risk of LLV and VLLV even after switching regimens

(Continued)

Table 5. (*Continued*)

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Chen, GJ, 2021[16] (*Cont.*)			Exclusion: Previous treatment failure to INSTIs PLWH with emergent genotypic resistance to dolutegravir		Patients in the DTG group were younger, virologically suppressed prior to inclusion for 5 years *versus* 6 years, and had higher rates of previous VF (53.3% *versus* 19.8% in the PI group) Of all VL tests in the observation period, 96 (7.1%) qualified for VLLV with 42 in the DTG group and 54 in the PI group; of all VL tests in the observation period, 43 (3.2%) qualified for LLV with 21 in the DTG group and 22 in the PI group	
Qin, S, 2021[14]	Retrospective follow-up on 1860 PLWH	Guangxi, China, 2003–2019	Inclusion: Available baseline VL data before ART initiation ART for at least 6 months Two or more VL records during follow-up Interval between VL test not more than 12 months Exclusion: Not matching inclusion criteria	VF defined as VL >400 copies/mL High LLV defined as 201–400 copies/mL Low LLV defined as 20–200 copies/mL	Participants enrolled had a mean age of 40 years and a median baseline VL of 4.89 $\log_{10}$ HIV-RNA copies/mL Cumulative incidence rates for VF were found to be insignificant for low LLV but significant for high LLV	Lopinavir and other PIs lead to higher rates of ART modification when compared to efavirenz ART modification is a VL high-risk factor for VF ($p<0.01$)

(Continued)

Table 5. (*Continued*)

Study authors	Study design	Location/ time frame	Pertinent inclusion/ exclusion criteria	Pertinent definitions	Results	Conclusions
Joya, C, 2019[17]	NHS Prospective, multicentre, open cohort with PLWH, 2006 PLWH were included, this analysis was a retrospective analysis	United States, 1996–2017	Inclusion: ART initiation during the study period who had at least 2 documented VL 6 months after initiation whilst on ART Exclusion: Those not meeting the inclusion criteria	LLV was defined as 50–199 copies/mL, high LLV was a VL of 200–1000 copies/mL LLV was subcategorized into iLLV and persistent LLV Continuous suppression was defined as VL <50 copies/mL VF was defined as >2 consecutive VL measurements of 200 copies/mL or more or any VL of >1000 copies/mL 6 months after initiation of ART	Participants enrolled had a median baseline VL of 4.5 $\log_{10}$ HIV-RNA copies/mL Definition of ART used was 2 NRTIs plus a third agent of either an INSTI, PI, NNRTI or third NRTI NNRTI-based regimens were most commonly initiated (49%) compared to unboosted PI (24%), INSTIs (11%) and boosted-PI (10%) 20% of included patients received mono or dual ARV prior to initiation of a triple regimen	Per this study, risk factors for VF included prior mono or dual ARV use (p<0.0001) and unboosted-PI regimens (p<0.0001) Per this study, risk factors for iLLV included initiating ART with an NNRTI or INSTI, and lower rates of mono or dual ARV use prior to initiation; iLLV was found to be protective against developing VF; therefore, the above are protective factors for VF but risk factors for iLLV

ART, antiretroviral therapy; ARV, antiretroviral; cART, combined antiretroviral therapy; DTG, dolutegravir; iLLV, intermittent low-level viraemia; INSTI, integrase strand transfer inhibitor; LLV, low-level viraemia; LTR, long terminal repeats; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NTUH, National Taiwan University Hospital; PI, protease inhibitor; PI/r, protease inhibitor boosted with ritonavir; PLWH, people living with HIV; SNAE, serious non-AIDS events; VF, virological failure; VL, viral load; VLLV, very-low-level viraemia; VS, virological suppression; WHO, World Health Organization.

deemed to have LLV, higher pre-treatment HIV RNA levels, lower CD4 cell counts and ART experience at baseline.[8,9,16,18] These risk factors were related to higher viral loads, the possibility of resistance forming especially in those who are ART experienced and an overall weakened immune system brought on by the duration of an unsuppressed viral load. In one of the studies, there was an inverse relationship between the number of viral load measurements taken and VF.[18] In theory, this may be due to more interaction between the healthcare provider and patient leading to increased monitoring that yields more frequent follow-up encounters. Nonetheless, making sure PLWH remain adherent to their medication regimen and undergo frequent monitoring until stabilization will assist in maintaining virological suppression and improving clinical outcomes.[36]

ART modification and adherence are factors that should also be addressed.[14,16] Prior to ART modification, healthcare providers can refer to the recommendations and see if modification is necessary prior to a switch. The healthcare provider should also monitor PLWH more regularly to assess adherence. More patient–practitioner interactions and a better relationship lead to higher medication adherence in PLWH.[37] Being adherent to ART leads to better viral load containment and increases in CD4 count, thus preventing opportunistic infections and cancers from occurring.[37–39]

Older age was associated with LLV and VF[8] yet another study found the inverse relationship[18] where age younger than 50 years was associated with a risk for developing LLV. One study showed that PLWH who were diagnosed prior to 2000 were at higher risk for developing VF and LLV. PLWH who were started on ART prior to 2000 were more likely to be using treatment regimens that faced many challenges such as high pill burdens, necessary high adherence, drug–drug interactions and adverse effects.[40] Over the years, preferred ART recommendations have changed, which may lead to PLWH modifying their ART regimen if their prior ART was discontinued. Additionally, prior to 1998, a rapid start approach was not an option or recommended and only recently became a more utilized way of treating PLWH, which may also contribute to the association of older age with LLV and VF.[8] Newer and better therapy options, such as INSTIs, second-generation NNRTIs or boosted PIs, have also paved the way for increased VS and treatment success by decreasing doses, increasing adherence and decreasing side effects; this may have been the reason for younger PLWH having better results than their older counterparts.[8] In a systematic search, it was found that PLWH of older age were more likely to be adherent to their medications than younger PLWH.[41] Further studies should be conducted to assess the specific risk factors associated with LLV and VF.

Another demographic that was found to be a risk factor was the Black race. One study did not find biological factors between regimens in Black or White PLWH but theorized that social factors were contributing to this disparity.[42] Another more recent study found medical mistrust in medication necessity among Black PLWH, where individuals believed that their medication does not keep them well nor does it prevent them from becoming sicker.[43] Both of these factors should be reassessed and addressed with the patient by building a better relationship between the medical team and the patient. Educating and empowering patients about their treatment regimen and the benefits of adhering to the medication can help mitigate mistrust of therapy.[44] Overall, common risk factors that should be observed more carefully in patients are high LLV, persistent LLV, ART adherence, higher pretreatment HIV RNA and lower CD4 cell counts.

NRTIs and NNRTIs are leading causes for first-line ART failure.[45] First-line treatment regimens recommend using INSTI plus one or two NRTIs.[12] Historic RNA GRT and proviral DNA GRT can be used to detect resistance mutations to prevent ART treatment failure. Using proviral DNA GRT was a viable alternative for an absent RNA GRT.[24] Even though guidelines[4,11] do not fully recommend the use of proviral DNA GRT and recommend caution when using these tests, it was also shown that RNA GRT can be used in instances of LLV because of newer testing methods with lower thresholds for detection with high success rates. In instances when historic RNA GRT was not available, proviral DNA GRT can be used to detect a resistance mutation. The current guidelines should be reconsidered when recommending all types of GRT as historic RNA GRT may not be available for every patient. Both RNA GRT and proviral GRT should be used in cases of LLV to have an inclusive list of all the mutations currently present and previously attained. These testing methods can also be used interchangeably with a high rate of success.[24] To prevent LLV and cases of VF, patients should test for resistance mutations to help guide treatment regimens and can be safely tested in cases of LLV.

Another test that may be useful in the management of LLV is next-generation sequencing (NGS), which has not been fully explored in reference to HIV and LLV but could provide clinicians with another tool to personalize treatment regimens. NGS can detect minority resistance variants at a lower threshold than the standard genotypic test.[46] Minority resistance variants have been thought to have clinical significance in negative outcomes of PLWH and LLV. NGS can also be cost effective as it can be largely scalable with testing in batches, thereby reducing costs. NGS can provide a more sensitive analysis of resistance mutations, and practitioners can modify medication regimens and maximize the outcome of ART. NGS has the potential to be beneficial in the treatment of PLWH, but this topic should be further explored once the standardization of NGS-based GRT has been accomplished.

Discrepancies exist between LLV classifications and definitions where there is no universal definition of LLV, making it difficult to study and compare in a clinical setting. The incidence of viral blips can range from 10% to 38%.[31,32,47] Viral blips are becoming more common with increasing efficacy in viral detection and with increasing awareness of viral blips. Viral blips are not a cause for changing of current ART, but they

are an indicator of the need for closer monitoring. Based on currently available data, viral blips are not an indicator or risk factor for VF.[18] Even though there were some conflicting studies saying blips contribute to VF, they were not the only factor. One study mentioned that a viral blip and at least three consecutive viral detections contributed to VF.[33] According to the definition of a viral blip, this would no longer be a blip and would be considered persistent LLV. This further demonstrates the importance of providing a uniform definition and range of viral levels for a more standardized comparison. One study showed that early ART initiation and lower HIV RNA levels at initiation were protective factors and PLWH who had a prolonged initiation time and high HIV RNA levels at the start showed a higher risk of developing viral blips,[32] indicating that early initiation will contribute to less frequent viral blips. This also provided some insight into latent reservoirs as a possible source of viral blips but further investigation is needed to confirm this. In the presence of a viral blip, PLWH should maintain the same regimen as there may be other factors that are causing the viral blip, such as biological fluctuations,[32] reactivation of latent reservoirs,[48] drug interactions or non-adherence.[27] These other factors should also be assessed when considering treatment. Overall, current studies found that true blips are unlikely to be associated with VF in LLV PLWH.[18,29]

In 2016, only 51% of PLWH had suppressed viral loads.[12] Suboptimal adherence is a strong predictor of poor viral response to ART that can lead to VF, transmission and resistance.[12] Patients who are non-adherent to ART require more frequent monitoring and accumulate costs.[12] Patients may be non-adherent for many reasons, including cost, undesired adverse effects, transportation issues (missed clinic appointments), depression, comorbidities and inconvenience (high pill burden, dosing frequency).[12] DHHS guidelines recommend assessing and counselling on patient adherence at every visit to reinforce the importance of maintaining VS.[12] Adherence can be strongly complicated by substance use disorders, homelessness and imprisonment.[12] Qin et al. discussed the impact of relationship status on adherence, disclosing that patients that are widowed or live alone have poorer adherence than those that cohabitate.[9] PI-based regimens may be useful for patients at risk for poor adherence or as an early start prior to resistance results due to their low likelihood of resistance even after a VF.[12] In a meta-analysis, depression was shown to be linked to ART non-adherence. Targeting early conversations about depression symptoms may improve adherence in patients.[13] Viral blips are common in successfully treated patients and are defined as patients having transient detectable viral loads (typically <200 copies/mL) followed by regression into undetectable viral loads.[11] Even highly adherent patients have a 10% chance of having a viral blip per year.[12] According to the DHHS HIV guidelines, viral blips are not associated or predictive of VF; however, the data between viral blips and consistent LLV are conflicting.[12] It is clear that adherence affects the probability of patients experiencing LLV but it is not clear if improving adherence could result in viral resuppression.[12] Nonetheless, adherence should be assessed and counselled for at every HIV follow-up visit to ensure optimal adherence (>80–95%).[12] Adherence was consistently reported as having an impact on LLV though it may be so in varying levels of HIV-VL (i.e. 50–199 copies/mL *versus* 200–999 copies/mL) and subsequent VF.[8,17,19–23]

Intensification of ART resulted in favourable virological outcomes with 10 out of 12 patients achieving VS and only 2 out of 12 remaining in persistent LLV (defined as two consecutive viral load measurements within 50–500 copies/mL in patients who had previously undetectable viral load measurements for at least 4 consecutive months on ARV); however, evidence may be obscured by the importance of genotyping for resistant mutations to ART. It is difficult to determine whether intensification of ART was responsible for the favourable outcomes or if it was the change to a medication without resistance mutations. LLV incidence declined in the 3-year study period when INSTIs were gaining confidence as a backbone ART regimen, possibly suggesting that INSTI-based ART regimens may increase rates of VS.[23] In a randomized controlled trial with a control and switch group, the switch group had poorer adherence to ART possibly due to the increased side effects from a new medication; however, the ART switch group still resulted in increased rates of VS.[34] A study conducted in sub-Saharan Africa evaluated the management of HIV in this patient population. In developing regions with high rates of HIV infection, genotyping and viral load measurements are not routine practices due to cost, leading to premature modification in ART regimens.[34] EACS guidelines recommend switching ART medications in certain situations, including documented side effects or prevention of long-term toxicity, drug–drug interactions, pregnancy, ageing/comorbidities, simplification, protection from hepatitis B virus, regimen fortification or cost reduction. It is suggested that all practitioners consider a patient's tolerability of their current regimen even if they have achieved VS.[11]

Conclusion

Studies defined VF and LLV with different viral load levels, which may lead to variances in results between the study groups. Studies also classified patients in different manners and used different HIV-RNA assays that can detect residual loads at different specificities, leading to differences in viral load reporting. One must be careful when comparing literature on this subject due to these differences. The current consensus is that LLV of less than 1000 copies/mL is relatively insignificant and should not warrant ART modification; however, emerging evidence discussed in this review proves differently and suggests the intensification of or switching to the next line ART regimen as beneficial for patients with persistent LLV. Persistent LLV levels of >200 copies/mL are associated with VF, serious AIDS events and increased mortality and should rationalize intensification of ART and lowering of the VF threshold of 1000 copies/mL (Table 5 and WHO

guidelines).[5,13,14,16,17,23,34,35] Furthermore, patients with higher baseline viral load measurements as well as lower CD4$^+$ T cell counts are at increased risk of LLV and subsequent VF.[5,8,16,17] It is important to note that lowering of the VF threshold will result in an increased demand for follow-up visits, viral load measurements and counselling resources, which in turn are likely to improve patient adherence and HIV-related outcomes. Lowering the LLV threshold would ultimately require more frequent lab testing and office visits, which could impact clinic workflow. Additionally, modifying ART regimens by moving onto second-line and third-line therapy options more quickly is a risk factor for poor HIV outcomes and growing resistance. New ART regimens come with new adverse events that may or may not affect patient medication adherence, which may further contribute to growing resistance. This strengthens the need for proper evaluation of LLV prior to intensification of ART regimens.

Although additional studies are needed on this very important clinical management topic, medication adherence should be confirmed first, then a thorough search for any potential drug interactions should take place, followed by a genotype resistance assessment, and lastly ART intensification, if indicated, based on the duration of LLV.

Key practice points

- Standardization in defining low-level viraemia (LLV) is needed.
- In patients who experience LLV, their medication adherence should be assessed, drug interactions reviewed and antiretroviral therapy intensified, if needed.
- Patients who experience LLV should be closely monitored for the development of virological failure.

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