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Management of low-level HIV viremia during antiretroviral therapy: Delphi consensus statement and appraisal of the evidence

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ABSTRACT

Objective While antiretroviral therapy (ART) is highly effective, detection of low levels of HIV-1 RNA in plasma is common in treated individuals. Given the uncertainties on the topic, we convened a panel of experts to consider different clinical scenarios, producing a Delphi consensus to help guide clinical practice.

Methods A panel of 17 experts in infectious diseases, virology and immunology rated 32 statements related to four distinct scenarios: (1) low-level viremia during stable (≥6 months) first-line ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL); (2) a viral blip during otherwise suppressive ART (a HIV-1 RNA measurement 50–1000 copies/mL with adjacent measurements <50 copies/mL); (3) low-level viral rebound during previously suppressive ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL); (4) residual viremia during suppressive ART (persistent HIV-1 RNA quantification below 50 copies/mL). A systematic review, conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement, informed the 32 statements. The Delphi procedure was modified to include two voting rounds separated by a moderated group discussion. Grading of Recommendations, Assessment, Development, and Evaluations-based recommendations were developed.

Results Overall, 18/32 statements (56.2%) achieved a strong consensus, 3/32 (9.4%) achieved a moderate consensus and 11/32 (34.4%) did not achieve a consensus. Across the four scenarios, the panel unanimously emphasised the importance of implementing specific interventions prior to considering therapy changes, including assessing adherence, testing for genotypic drug resistance and scheduling more frequent follow-up visits. Strategies indicated in selected circumstances included therapeutic drug monitoring, quantifying total HIV-1 DNA and evaluating concomitant chronic infections.

Conclusions While acknowledging the many uncertainties about source, significance and optimal management of low-level viremia during ART, the findings provide insights to help harmonise clinical practice. There is a need for well-designed randomised studies assessing different interventions to manage low-level viremia and future research regarding its definition.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well established that antiretroviral therapy (ART) effectively suppresses HIV-1 replication, leading to virological suppression in most individuals. However, low-level viremia (LLV), characterised by persistently or intermittently detectable low levels of HIV-1 RNA in plasma despite good adherence to ART, is a common clinical finding. The interpretation and management of LLV vary due to limited evidence supporting optimal strategies.

WHAT THIS STUDY ADDS

⇒ This project provides valuable insights into the management of LLV during ART. We conducted a consensus development study involving a panel of experts to address the lack of evidence-based guidelines. Through a systematic review and analysis of available data, this study identifies common clinical scenarios of LLV and proposes interventions tailored to each scenario. Key findings include recommendations on ART regimen modification, genotypic resistance testing, adherence assessment, therapeutic drug monitoring and follow-up strategies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study offer practical guidance for clinicians in managing LLV during ART, addressing the uncertainties and variations in clinical practice. By providing evidence-based recommendations and suggestions, it helps standardise approaches to LLV management, potentially improving patient outcomes. Additionally, the study highlights the need for further higher quality studies to fill knowledge gaps and refine management strategies.

INTRODUCTION

Antiretroviral therapy (ART) is highly effective in suppressing HIV-1 replication and most individuals receiving currently recommended regimens achieve virological suppression.[1 2] Despite this success, HIV

Table 1 Definitions of plasma HIV-1 RNA detection during ART according to different guidelines and the Low-Level HIV Viremia Consensus Panel

	EACS[4]	JAMA/IAS[5 6]	HIVinfo.gov/DHHS[8]	WHO[7]	LLHV-CP
Residual viremia	Not defined	HIV RNA levels>20 and <50 copies/mL[6]	Not defined	Not defined	Quantifiable HIV-1 RNA levels below 50 copies/mL.
Low-level viremia	HIV RNA levels>51 and <200 copies/mL	HIV RNA levels 50–200 copies/mL[5 6]	Confirmed detectable HIV RNA levels<200 copies/mL	HIV RNA levels 50–1000 copies/mL	≥2 consecutive HIV RNA measurements between 50 and 500 copies/mL.
Viral blip	Not defined	An outlier increase in HIV RNA levels to<1000 copies/mL that returns to undetectable levels[5]	After vs, an isolated detectable HIV-RNA level that is followed by a return to vs	An isolated HIV-RNA measurement of 50–1000 copies/mL with a return to suppressed levels	A single HIV-1 RNA measurement between 50 and 1000 copies/mL with adjacent measurements<50 copies/mL.
Viral rebound	Confirmed HIV RNA levels>50 copies/mL in someone with previously undetectable viremia	Not defined	After vs, confirmed HIV RNA levels≥200 copies/mL	Not defined	Confirmed HIV-1 RNA>50 copies/mL following previously suppressed viremia.

ART, antiretroviral therapy; DHHS, Department of Health and Human Services; EACS, European AIDS Clinical Society; JAMA/IAS, Journal of American Medical Association/International Antiviral Society; LLHV-CP, Low-Level HIV-1 Viremia Consensus Panel; VS, viral suppression.

cannot be eradicated due to the persistence of latently infected cells containing stably integrated HIV-1 DNA.[3]

In the course of effective ART, some individuals experience persistently or intermittently detection of low HIV-1 RNA levels in plasma despite reporting excellent adherence. Various definitions based on magnitude and persistence are used internationally to describe plasma HIV-1 RNA detection, including residual viremia (RV), low-level viremia (LLV) and viral blip (VB) (table 1).[4–8] The interpretation and recommended management vary, reflecting the limited evidence base for this common clinical finding.[9]

In individuals with excellent adherence, the source of plasma HIV-1 RNA is probably multifactorial.[2] HIV-1 RNA sequences in plasma typically do not evolve over time, with most evidence attributing the source of plasma HIV-1 RNA to bursts of viral production from memory CD4+ T cells harbouring integrated provirus, with ART immediately blocking further replication.[10] One additional mechanism may involve ongoing virus replication due to suboptimal drug potency or exposure or within sanctuary sites characterised by reduced drug penetration and exclusion of immune response.[11] Differentiating between these scenarios is important, as changing the ART regimen would only be effective in cases of ongoing virus replication.

Several interventions can be considered in the management of LLV, including investigations of adherence, drug resistance, HIV-1 DNA load (as a measure of the viral reservoir), chronic coinfections, plasma drug concentrations and inflammatory markers. Intensified monitoring with more frequent follow-up visits is common practice, and for some individuals, ART changes may be considered. As clinical practice varies, we conducted a consensus development project based on a modified Delphi procedure, with support from a systematic review (SR) employing a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)-based approach.

METHODS

The study was conducted over a 2-month period (figure 1). Initially, a SR employing a GRADE approach was conducted to identify clinical scenarios (CS) related to detection of plasma HIV-1 RNA at low copy numbers and its multiple definitions available in the literature and support panel's recommendations. The identified CS were: (1) LLV during stable (≥ 6 months) first-line ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL); (2) a VB during otherwise suppressive ART (a HIV-1 RNA measurement 50–1000 copies/mL with adjacent measurements <50 copies/mL); (3) low-level viral rebound during previously suppressive ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL); (4) RV during suppressive ART (persistent HIV-1 RNA quantification below 50 copies/mL). Eight interventions for the management of each CS were assessed by the review, and respective statements were formulated, considering currently recommended oral ART regimes and excluding the use of long-acting injectable therapy. Statements concerning the proposed interventions included: (a) ART regimen modification; (b) genotypic resistance testing (GRT); (c) assessment of adherence; (d) performing therapeutic drug monitoring (TDM); (e) scheduling an earlier follow-up; (f) evaluating chronic coinfections; (g) assessing inflammatory markers; (h) quantification of HIV DNA in peripheral blood.

The search question and full-research protocol for the SR are available on PROSPERO (CRD CRD42024511492). The full methodology and results from the SR are reported in a separate publication.[12]

To determine recommendations for the management of the identified CS, we employed a modified Delphi procedure, where an expert panel of 17 HIV specialists was consulted and chosen based on expertise in Infectious Diseases, Virology and Immunology, current direct involvement in HIV care and engagement in the topic as indicated by field of research and scientific output. The procedure included two Delphi rounds separated by a group discussion moderated by MA and CFP.

The Delphi method,[13] a consensus-building approach,[14] involved collecting opinions through a procedure ensuring: (a) anonymity—the experts did not know the responses of the other specialists; (b) feedback—the experts could suggest additional

Figure 1 Flowchart of the development of the scenarios, statements and suggestions.

information for research or justify their choices; (c) iterations—the number of rounds and (d) statistical analysis.[15]

Experts were invited to review the content of each scenario and the statements linked to it and to rate each one in terms of its validity and relevance by indicating a value from 1 to 5 on a Likert scale, where 1=strongly disagree (*I do not agree with this statement in the context of this scenario*) and 5=strongly agree (*This statement is relevant and I agree in the context of this scenario*). At the end of the first round, the mean and SD, as well as the content validity index (CVI), were calculated for each statement.[16] Furthermore, Cronbach's alpha was calculated for each scenario.[17 18] Content validity determines the ability of the selected items to reflect the variables of the construct in the measure, addressing the degree to which the items of an instrument sufficiently represented the content domain. This could be quantified through the CVI, deriving from the ratio between number of experts that rate a singular item with 4 and 5 (maximum rates) and the total number of experts involved. CVI ranges from 0 to 1 or from 0 to 100%. A CVI greater than 70% is deemed to be suggestive of the item's consensus, a rate above 75% is considered indicative for strong consensus, while a rate lower than 70% is deemed to be suggestive of non-consensus.[16] Experts were also asked to rank each statement based on the clinical priority in order to manage every CS.

Subsequently, the panel of experts gathered to discuss the scenarios and statements during a 2-day meeting. Facilitators went through all the scenarios and statements, presenting the results of the first round of Delphi, and receiving comments and suggestions from the panel with the aim of modifying the statements with poor agreement. After collecting and incorporating all the suggestions, the modified version of the document was sent to the panel of experts for a second round of Delphi, resulting in the final version of the document with the recommendations.

The full expert panel and their role of expertise are available in online supplemental file 1.

RESULTS

The outcome of the final Delphi round, level of agreement, consensus results and CVI are provided in table 2. After the second round, 18/32 (56.2%) statements achieved strong consensus, 3/32 (9.4%) reached moderate consensus and 11/32 (34.4%) statements did not achieve consensus. The level of priority assigned to each proposed intervention is reported in figure 2.

Statement 1: immediate need to modify the ART regimen

Data identified from SR

The systematic search identified 14 studies evaluating the topic, including three randomised controlled trials (RCTs).[19–21]

The meta-analysis of four cohort studies,[22–25] reporting virologic suppression (defined as <20 cp/mL) among a total of 435 people with HIV (PWH) with LLV who switched therapy and 532 PWH with LLV who belonged to the non-intervention group, reported no significant association between therapeutic switch and virologic suppression. The meta-analysis of three studies (one RCT, one cohort and one case–control) reporting virologic suppression (defined as <50 cp/mL) in a total of 121 PWH with LLV who switched therapy and 192 PWH with LLV who continued therapy, also reported no significant association between therapeutic switch and virologic suppression.[21 26 27]

Among the studies that could not be meta-analysed a non-randomised study and an RCT report that treatment intensification of ART with raltegravir did not decrease the rate of RV in subjects on ART.[20 28] A French study investigating a switch to a dual therapy based on maraviroc and raltegravir did not find a correlation with reducing RV.[29] Another non-randomised study found that RV was not reduced by ART intensification.[30] Conversely, a beneficial effect of an ART switch in PWH with RV was reported in two studies.[19 31] A cohort study conducted on PWH with LLV found a virologic suppression in 20/27 cases after ART modification.[32]

Panel's consensus and management suggestions

The panel suggests against an immediate treatment change in the four CS considered, with high CVIs of 94%–100% for scenarios 1, 2 and 4, decreasing to 76% for scenario 3 (*weak recommendation, very low certainty of evidence*).

Statement 2: perform genotypic resistance testing

Data identified from SR

Available data derived from observational studies with sample sizes ranging from 18 to 2200, where GRT was conducted on plasma with HIV-1 RNA levels ranging from 20 to 1000.[23 26 32–47] The meta-analysis of 19 studies including 7508 PWH on ART with LLV showed an overall drug resistance of 28.74% (95% CI 27.84 to 29.65). A meta-analysis of three cohort studies conducted in 406 participants with LLV concluded that PWH with LLV who have drug resistance documented by GRT are significantly less likely to achieve virological suppression. Other studies have reported mainly resistances in gag,[48] new resistance mutations in 37% of these participants during LLV[34] and a resistance prevalence of 74% analysing 3895 samples from 2200 patients.[46]

Panel's consensus and management suggestions

The panel suggests performing GRT in scenarios 1 and 3, while does not suggest performing GRT in scenario 2 and scenario 4 (CVI=1:82%; 2:100%; 3:100%; 4:70%) (*weak recommendation, very low certainty of evidence*).

Statement 3: assess adherence

Evidence identified from SR

The literature search identified a total of 11 studies on the topic. The meta-analysis of 5 cohort studies among 306 PWH with LLV reported an overall prevalence of suboptimal adherence to ART of 38.05% (95% CI 32.7 to 43.3). The effect of counselling on improving adherence and in turn reducing LLV was reported by two studies.[49 50]

Lower adherence was significantly associated with LLV in a French case–control study, another one in Canada and a third cohort study in Italy.[51–53] On the other hand, an Italian study concludes that adherence above 70% was enough to maintain viral suppression stating that an elevated regimen forgiveness may be an important feature, next to adherence, to improve patient outcomes.[54] On the contrary, reported adherence was similar among PHW with and without LLV in a prospective cohort study in Peru and a case–control study in the USA.[55 56]

Panel's consensus and management suggestions

The panel suggests assessing adherence to ART during the management of all scenarios considered (CVI=1:100%; 2:100%; 3:100%; 4:94%) (*strong recommendation, very low certainty of evidence*).

Table 2 Statements and panel consensus

Number	Statement	CVI*	Agreement range	Mean	Consensus
Scenario 1. Low-level viremia during stable (≥6 months) first-line ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL)					
1	Immediate need to modify the ART regimen	100	1–2	1.3	Strong consensus against
2	Perform GRT	82	2–5	4.3	Strong consensus in favour
3	Assess adherence	100	5	5	Strong consensus in favour
4	Perform TDM	58	2–5	3.4	No consensus
5	Schedule an earlier follow-up	100	4–5	4.8	Strong consensus in favour
6	Evaluate chronic coinfections	58	2–5	3.6	No consensus
7	Assess inflammatory markers	76	1–4	2.2	Strong consensus against
8	Quantify HIV DNA in peripheral blood	76	1–5	3.6	Strong consensus in favour
Scenario 2. A viral blip during otherwise suppressive ART (a HIV-1 RNA measurement 50–1000 copies/mL with adjacent measurements<50 copies/mL)					
1	Immediate need to modify the ART regimen	100	1–2	1.1	Strong consensus against
2	Perform GRT	100	1–2	1.6	Strong consensus against
3	Assess adherence	100	4–5	4.9	Strong consensus in favour
4	Perform TDM	82	1–4	1.9	Strong consensus against
5	Schedule an earlier follow-up	88	2–5	4.3	Strong consensus in favour
6	Evaluate chronic coinfections	47	1–5	3.2	No consensus
7	Assess inflammatory markers	100	1–2	1.5	Strong consensus against
8	Quantify HIV DNA in peripheral blood	64	1–4	2.2	No consensus
Scenario 3. Low-level viral rebound during previously suppressive ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL)					
1	Immediate need to modify the ART regimen	76	1–5	2.2	Strong consensus against
2	Perform GRT	100	4–5	4.9	Strong consensus in favour
3	Assess adherence	100	4–5	4.9	Strong consensus in favour
4	Perform TDM	58	2–5	3.6	No consensus
5	Schedule an earlier follow-up	88	2–5	4.4	Strong consensus in favour
6	Evaluate chronic coinfections	53	2–5	3.3	No consensus
7	Assess inflammatory markers	70	1–4	2.5	Moderate consensus against
8	Quantify HIV DNA in peripheral blood	58	2–5	3.4	No consensus
Scenario 4. Residual viremia during suppressive ART (persistent HIV-1 RNA quantification below 50 copies/mL)					
1	Immediate need to modify the ART regimen	94	1–5	1.3	Strong consensus against
2	Perform GRT	70	1–4	2.4	Moderate consensus against
3	Assess adherence	94	2–5	4.6	Strong consensus in favour
4	Perform TDM	64	1–5	2.4	No consensus
5	Schedule an earlier follow-up	70	2–5	3.8	Moderate consensus in favour
6	Evaluate chronic coinfections	41	1–5	3.2	No consensus
7	Assess inflammatory markers	64	1–4	2.4	No consensus
8	Quantify HIV DNA in peripheral blood	47	1–4	3.1	No consensus

Levels: 1, disagree; 2 somewhat disagree; 3 almost agree; 4, agree; 5, strongly agree.
*CVI expressed as %.
ART, antiretroviral therapy; CVI, content validity index; GRT, genotypic resistance testing; TDM, therapeutic drug monitoring.

Statement 4: perform TDM

Evidence identified from SR

The SR identified three studies on the topic. A Canadian cohort study measured subtherapeutic drug concentrations in 78/328 (24%) treated individuals with HIV-1 RNA levels between 50 and 999 copies/mL.[33] In contrast, an observational study in Peru found no difference in nevirapine concentration among 33 adherent individuals with and 49 adherent individuals without LLV, defined as HIV-1 RNA levels of 30–1000 copies/mL.[55] Finally, a French prospective cohort study concluded that plasma drug concentrations were adequate in 53/57 (93%) individuals with HIV-1 RNA levels between 21 copies/mL and 200 copies/mL).[22]

Panel's consensus and management suggestions

The panel suggests against routine use of TDM in the management of scenario 2, whereas no consensus was reached for any of the other scenarios (CVI=1:58%; 2:82%; 3:58%; 4:64%) (*weak recommendation, insufficient evidence*).

Statement 5: schedule an earlier follow-up

Evidence identified from SR

The SR did not identify evidence on the topic.

Panel's consensus and management suggestions

The panel suggests scheduling an early follow-up visit for scenarios 1, 2, 3 (CVI=1:100%; 2 and 3:88%) and for scenario 4 (CVI=70%) (*weak recommendation, no evidence identified*).

Statement 6: evaluate chronic coinfections

Evidence identified from SR

No studies addressing this issue were identified in the SR.

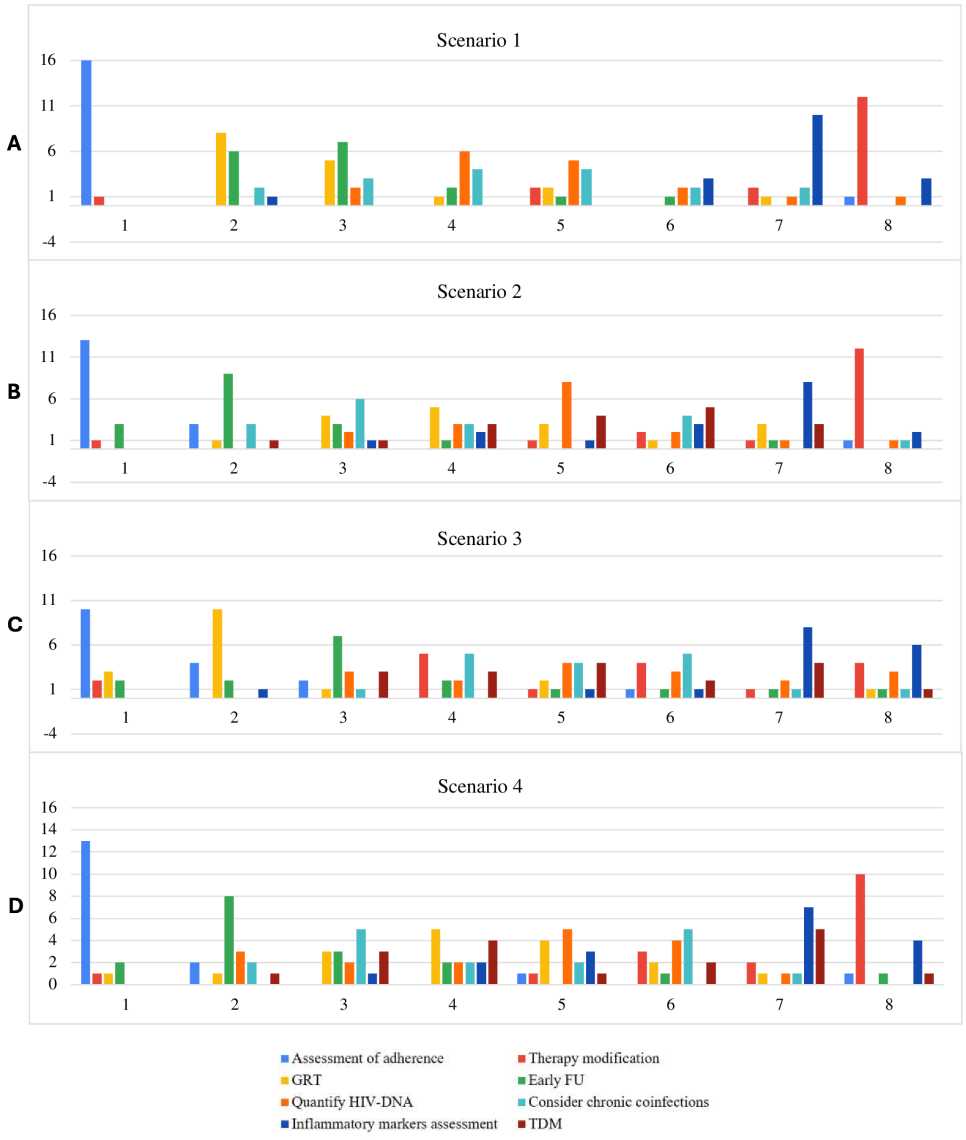

Figure 2 . Opinion on the priority of interventions in the management of people with low-level viremia during ART. (A) Scenario 1. Low-level viremia during stable (≥6 months) first-line ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL); (B) Scenario 2. A viral blip during otherwise suppressive ART (a HIV-1 RNA measurement 50–1000 copies/mL with adjacent measurements <50 copies/mL) (C) Scenario 3. Low-level viral rebound during previously suppressive ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/ml); (D) Scenario 4: Residual viremia during suppressive ART (persistent HIV-1 RNA quantification below 50 copies/mL). ART, antiretroviral therapy; GRT, genotypic resistance testing; TDM, therapeutic drug monitoring; FU, follow-up.

Panel's consensus and management suggestions

The panel debated the potential role of coinfections such as chronic hepatitis B or cytomegalovirus in driving LLV. However, no consensus was reached in any of the four scenarios (CVI=1 58%; 2 47%; 3 53%; 41%).

Statement 7: assess inflammatory markers

Evidence identified from SR

The search identified four relevant observational studies on the topic. No correlation was found between LLV (HIV-1 RNA 20–399 copies/mL) and a series of inflammation markers in a cohort study in the USA[57] and in Africa.[58] A correlation between viremia and growth differentiation factor 15 and D-dimer was found in a Swedish case–control study, while there was no correlation with C reactive protein (CRP) interferon-inducible protein 10 (IP-10) or soluble CD-14.[59] In a Spanish cross-sectional study (n=52), microbial translocation and levels of Tumour Necrosis Factor alpha (TNF-alpha) and IL-6 were higher in the presence of HIV-1 RNA levels between 20 copies/mL and 200 copies/mL compared with levels<20 copies/mL.[60]

Panel's consensus and management suggestions

The panel suggests against routine assessment of inflammatory markers (other than CD4+, CD8+ T cell count and ratio) such as IL-6 and CRP in the management of scenarios 1, 2 and 3 (CVI=1:76%; 2:100%; 3:70%); no consensus was achieved for scenario 4 (CVI=64%) (*weak recommendation, insufficient evidence*).

Statement 8: quantify HIV-1 DNA in peripheral blood

Evidence identified from SR

The SR identified limited evidence on this topic. In a single-arm pilot study in the USA, the level of viremia was positively

associated with the amount of reservoir, measured by infection units per million cells.[61] Another study showed no significant correlation between HIV-1 DNA levels and detection of HIV-1 RNA levels, in terms of Target Not Detected and RV development among virologically suppressed participants who either continue dolutegravir plus one Reverse Transcriptase Inhibitor (RTI) or switch to coformulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide E/C/FTC/TAF.[19] In contrast, a cross-sectional study in Canada (n=127) demonstrated a correlation between RV and the frequency of CD4+cells carrying HIV-1-integrated DNA.[62]

Panel's consensus and management suggestions

The panel suggests measuring total HIV-DNA load in peripheral blood, in scenario 1 (CVI=1:76%); no consensus was reached for the other scenarios (CVI=2:64%; 3:58%; 4:47%) (*weak recommendation, insufficient evidence*).

DISCUSSION

LLV is common in clinical practice, but there is limited evidence to guide management strategies. In an attempt to support harmonised practice, we defined four common CS characterised by LLV, accompanied by a description of possible interventions. These were discussed within a panel of experts following a modified Delphi procedure. The consensus was developed through a 2-day discussion with a focus group in between, providing the experts with the findings of the SR to enrich the confrontation. Where applicable, GRADE-based recommendations were developed.

The panel expressed a consensus that an accurate evaluation should be performed in all cases before considering a change of ART. Such consideration should always begin with a thorough assessment of adherence. However, the urgency of considering a change of the ART regimen was also related to type of CS and the regimen. For example, a more rapid decision about modifying the ART regimen should be considered in scenario 3, that is, a case of virological rebound at LLV, especially in the case of regimens with a low barrier to the emergence of resistance.

The panel reached a strong consensus on undertaking GRT testing in cases of LLV during stable (≥6 months) first-line ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL) and LLV rebound during previously suppressive ART (≥2 consecutive HIV-1 RNA measurements 50–500 copies/mL). In the former scenario, incomplete agreement was driven by the consideration that ART-naïve subjects with high pre-ART viral load may take longer to achieve viral suppression, without necessarily acquiring resistance. The panel also agreed unanimously that GRT is not indicated in VB or RV, but should be reserved for confirmed viremia above 50 copies/mL. However, the discussion highlighted that the approach to VB should be related to their magnitude and frequency. In one study, for instance, VB >500 copies/mL were associated with an increased risk of virological failure.[63] Thus, larger or more frequent blips should trigger a review of adherence and consider the risk of emergent drug resistance. The SR identified several studies indicating that performing GRT is possible and likely to reveal the presence of resistance-associated mutations (RAM) in a substantial fraction of individuals with LLV, although not all studies differentiated between pre-existing and treatment-emergent RAMs.[23 26 32–47] However, resistances are less frequent with the current first-line antiretroviral regimens. In the setting of LLV, sequencing of cellular material, rather than plasma, may offer an alternative tool.[4 8 38 64 65]

Regarding the assays to be used in case of LLV, plasma GRT performed through the bulk sequencing provides reliable and reproducible results that are informative about emerging drug resistance[43 46 66] and predictive of the subsequent virological failure.[47] However, this assay could not be always successful at LLV. HIV GRT through next-generation sequencing (NGS) is gradually replacing bulk sequencing. Nowdays, through NGS approaches, is possible to detect low-abundance drug-resistance mutations.[67] On the other hand, NGS has specific limitations regarding the virion copies used as input, which may make them unsuitable for GRT when HIV-1 RNA levels are below 1000 copies/mL. Resistance GRT performed on peripheral blood mononuclear cells is technically feasible and can represent a valuable tool to define drug-resistance profiles archived in HIV-DNA.[64 65] Therefore, in case of unsuccessful plasma GRT, HIV DNA GRT may also be considered. However, this assay may not detect previous resistance mutations and can also detect clinically irrelevant mutations; thus, the results should be interpreted with caution. NGS methods might improve resistance detection in HIV-DNA due to their greater sensitivity.[68] So far, most clinical applications of NGS have used thresholds between 5% and 10%, however further studies are needed to evaluate the most clinically relevant threshold for NGS. In any case, when a therapy switch is planned, in combination with the GRT performed at LLV, cumulative genotypic resistance history should be always considered together with a complete history of ART and viremia.[4 8]

The panel agreed about the relevance of plasma drug concentrations in driving outcomes but highlighted limitations related to TDM test availability and interpretation. This resulted in lack of a consensus in most scenarios, although testing should be considered in specific cases, for example, suspected malabsorption or drug–drug interactions. As of now, routine TDM is not recommended. However, it may be beneficial in cases involving drug interactions, toxicity control, special populations (eg, children, pregnant individuals and the elderly) or in managing treatment responses in patients with good adherence but suboptimal outcomes.[22 69]

The panel recognised the potential impact on HIV pathogenesis of chronic coinfections such as hepatitis B or cytomegalovirus.[70 71] However, there was lack of consensus about how to use the information to guide the management of LLV in routine practice, beyond recommending that such infections should be appropriately managed. On the other hand, the panel recognised the importance of considering intercurrent infections or vaccinations in relation to the occurrence of VBs.[72–74]

Along similar lines, experts recognised the pathogenic role of inflammation and immune activation and discussed how they may both result from and be a driver of viremia.[75–77] Beyond the routine evaluation of CD4+, CD8+ count and ratio as easily available, most members acknowledged the difficulties of implementing wider inflammatory biomarker assays due to lack of consensus on the type of markers to adopt in routine practice, interpretation, availability and costs.

The panel discussed the potential role of total HIV-1 DNA quantification, as VBs and LLV are significantly associated with slower reservoir decay.[78] One recognised limitation was access to standardised tests.[79]

For the majority of the statements considered, the SR identified low-quality studies, often lacking a direct comparison of populations with and without LLV. Included studies were frequently not powered to identify our outcome of interest, hence indirectness was an issue in almost all the studies. Furthermore, most of the studies included a low number of

participants and were downgraded for high level of imprecision. In this context, even when a strong consensus was reached by the panel of experts, the recommendations or suggestions put forth should be cautiously framed, hence providing weak recommendations/suggestions and emphasising the need for future studies that are appropriately designed and of higher quality.

CONCLUSION

LLV during effective ART is multifactorial. Beyond continued monitoring for evidence of increasing viral load, we currently have limited tools to differentiate between virus release from reservoirs and ongoing virus replication, making clinical management challenging. While research on new technologies is ongoing,[80] LLV requires a personalised approach, taking into consideration the individual-related factors and utilising diagnostic tools judiciously. Further research is warranted to address the knowledge gaps, starting from agreeing on definitions. The suggestions outlined in this study aim to assist clinicians in navigating the complexities of managing LLV during ART.

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Supplementary Material 1. Panel members and their area of expertise.

Panel member	**Role**
Prof. Massimo Andreoni	Senior ID Specialist - Chair
Prof. Carlo Federico Perno	Senior Virologist - Chair
Prof. Francesca Ceccherini-Silberstein	Senior Virologist
Dr. Mirko Compagno	ID Specialist
Prof. Andrea Cossarizza	Senior immunology scientist
Prof. Antonio Di Biagio	Senior ID Specialist
Dr. Luna Colagrossi	Senior Virologist
Prof. Anna Maria Geretti	Senior ID Specialist and Senior Virologist
Prof. Nicola Gianotti	Senior ID Specialist
Prof. Andrea Gori	Senior ID Specialist
Prof. Sergio Lo Caputo	Senior ID Specialist
Prof. Giulia Marchetti	Senior ID Specialist
Prof. Claudio Mastroianni	Senior ID Specialist
Prof. Cristina Mussini	Senior ID Specialist
Prof. Mariella Santoro	Senior Virologist
Prof. Loredana Sarmati	Senior ID Specialist
Prof. Maurizio Zazzi	Senior Virologist