Guidance on the clinical management of HIV-1 persistent low-level viraemia on antiretroviral treatment: a scoping review and an international Delphi consensus

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Despite the success of antiretroviral therapy, a subset of people with HIV experience low-level viraemia (LLV), a challenging condition with inconsistent definitions and management across settings. We conducted a scoping review of the literature and developed international consensus recommendations through a modified Delphi process involving a multidisciplinary panel of experts. Available evidence shows wide variability in definitions of persistent LLV, most commonly encompassing repeated viral loads between 50 and 1000 copies per mL. Outcomes associated with LLV are heterogeneous. Despite associations between LLV at 50–200 copies per mL and virological failure of more than 1000 copies per mL, resistance emergence or adverse clinical outcomes are inconsistent; stronger evidence links LLV of 200–1000 copies per mL to these endpoints. Based on these findings, we propose a pragmatic management framework that includes prompt confirmation of LLV, assessment of adherence and drug interactions, consideration of resistance testing (especially at viral loads of 200–1000 copies per mL), a broader clinical evaluation, individualised treatment optimisation (according to viral load strata, the genetic barrier to resistance of current and potential antiretroviral regimens, and the HIV resistance profile), and individual prevention strategies for viral loads of 200–1000 copies per mL. This international guidance aims to support clinicians in identifying when LLV requires action, reduce variability in clinical practice, and inform management strategies across diverse health-care settings.

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Introduction

Although the recent crisis in international HIV funding raises concerns about the achievement and sustainability of the UNAIDS 95–95–95 targets, the scale-up of antiretroviral therapy (ART) has enabled substantial progress in suppressing HIV-1 RNA concentrations below levels associated with disease progression or transmission. However, full suppression on ART is not always reached or maintained; some people present with low-level viraemia (LLV; 3–26% of people depending on setting), which can result from difficulty with adherence, biological factors, or both, although the underlying mechanisms remain incompletely understood.[1–6]

LLV is generally defined as multiple viral load measurements above the level of detection but below the threshold for unequivocal virological failure, which varies across settings from over 50 to over 1000 copies per mL.[7–12] Although viraemia is a continuous biological metric without natural cutoffs, operational thresholds reflect the need for clinically actionable definitions. WHO defines LLV as 50–1000 copies per mL. Guidelines from some upper-middle-income countries are aligned with this definition (eg, Southern African HIV Clinical Society),[11] whereas others adopt alternative thresholds and subcategories, such as Sociedad Argentina de Infectología guidelines, which distinguish very low-level viraemia at 50–200 copies per mL from LLV at 200–500 copies per mL.[12] In contrast, high-income country (HIC) guidelines (eg, the European AIDS Clinical Society, US Department of Health and Human Services, and International Antiviral Society–USA) typically define LLV as less than 200 copies per mL, with lower thresholds ranging from the assay's limit of detection to 50 copies per mL.[7–10] However, viral loads detectable below 50 copies per mL are generally referred to as residual viraemia instead of LLV. Variability in LLV definitions also partly reflects technical factors: advances in viral load platforms have introduced some degree of analytical variability and increased the detection of low-level signals, many of which might not represent clinically meaningful viraemia.[13] Differences across assays in calibration and reporting units (copies per mL *vs* international units per mL) could further affect comparability, particularly at low viral loads.

LLV might result from viral production originating from the latent reservoir. This production can arise from transcriptionally active defective proviruses, which generate non-infectious virus, or from replication-competent proviruses, which produce infectious virus. These viruses most likely originate from clonally expanded lymphocytes harbouring proviral DNA. In such cases, treatment modification fails to reduce viral load, which is known as non-suppressible viraemia.[14–18] Alternatively, LLV could reflect ongoing replication, exposing people to the risk of progressive viral load increase and resistance emergence.[14] This hypothesis is supported by the decline in LLV frequency that is observed with second-generation integrase inhibitors, suggesting that residual replication under less potent regimens previously contributed to low-level viraemia.[4] In clinical

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practice, both mechanisms can coexist within a person,[14,19] and differentiating between them remains diagnostically challenging. These findings raise concerns about the potential detrimental effects of LLV on virological failure, resistance selection, immune activation, and transmissibility (figure 1). It remains unclear what level of viraemia entails substantial risk for resistance evolution or transmission, whether the genetic barrier to resistance of the ongoing antiretroviral regimen modifies these risks, and to what extent LLV contributes to CD4 cell loss, inflammation, and morbidity. Although a 2023 systematic review found no documented HIV sexual transmissions at viral loads of less than 600 copies per mL,[20] infectivity studies have shown a very low per-act risk at 1000 copies per mL.[21] WHO recommendations acknowledge that transmission risk approaches zero at a viral load of less than 1000 copies per mL;[22] however, the need for additional prevention strategies at the individual level when viral load is 200–1000 copies per mL remains uncertain.

Due to differences in health-care infrastructure, diagnostic capacity, ART availability, and definitions of virological failure, LLV might not be prioritised equally across settings. The trade-offs involved in detecting and addressing LLV are context dependent. In low-income and middle-income countries (LMICs), several specific barriers persist, including variable virological failure definitions leading to different LLV thresholds, insufficient access to virological and treatment monitoring, and restricted therapeutic options that preclude individualised management. These constraints limit the feasibility of LLV-focused interventions, even though a failure to identify and prioritise LLV can delay necessary actions and increase the risk of adverse clinical outcomes. Currently, numerous diagnostic and therapeutic interventions could be considered in the case of LLV, including adherence counselling, genotypic resistance testing, drug exposure testing, immune profiling, cerebrospinal fluid analysis (in the presence of neurological or neuropsychiatric symptoms or cognitive impairment), and regimen switching to improve genetic barrier or compartment penetration. Importantly, some of these interventions (eg, adherence counselling and treatment optimisation) are low cost and potentially feasible in most settings.

Although local initiatives have attempted to address aspects of LLV management,[23,24] these efforts are not yet supported by a comprehensive and globally harmonised framework. Consequently, the heterogeneity of definitions, variability in available evidence, and differences across health-care settings have resulted in substantial uncertainty and inconsistency in the clinical management of LLV.

To address these key gaps, we performed a scoping review of published work and developed consensus recommendations based on this review and feedback from an international panel of experts (appendix pp 2–7) to guide the definition and clinical management of LLV across diverse health-care settings.

Methods

Scoping review

We conducted a scoping review on the topic of HIV LLV during ART according to PRISMA guidelines (appendix pp 8–9). The initial study protocol was prospectively registered with PROSPERO (CRD42023491303). We

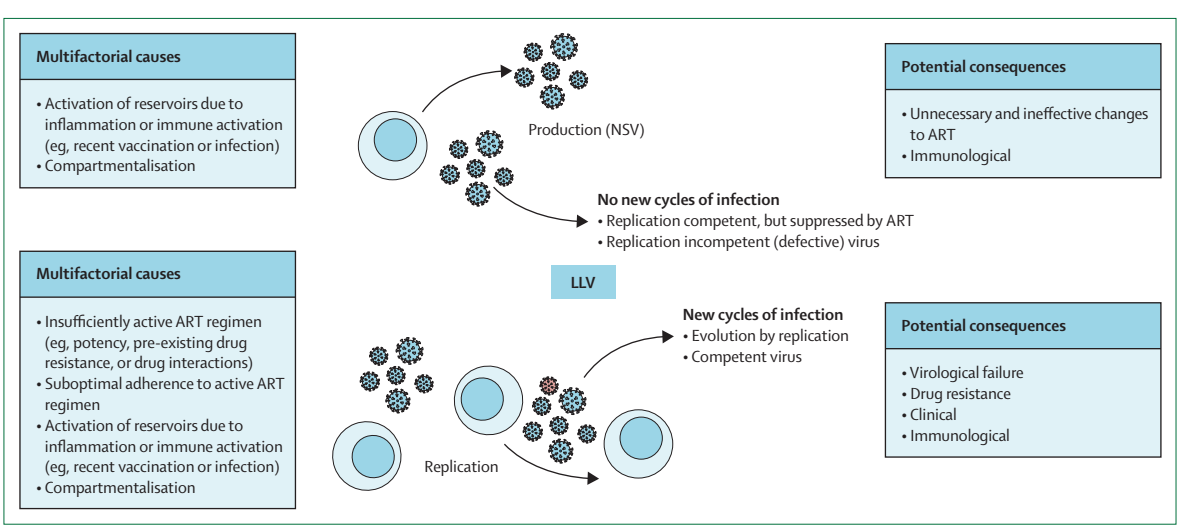

Figure 1: **Mechanisms and consequences of LLV**
LLV has multifactorial causes and can either be the result of viral production, replication, or both. During viral production, a latently infected cell is activated and produces viral RNA, proteins, or HIV particles, but new cells do not become infected due to the presence of ART or because the produced virus is replication incompetent (defective). However, ART does not prevent the production of viral particles or viral RNA, which is known as non-suppressible viraemia. During viral replication, new CD4 cells become infected and new replication cycles occur, resulting in viral evolution. ART=antiretroviral therapy. LLV=low-level viraemia. NSV=non-suppressible viraemia. Figure created with BioRender.com.

searched PubMed (MEDLINE), Cochrane Central Register of Controlled Trials, and Embase for articles published in English from Dec 1, 2008, to Jan 1, 2025 (appendix pp 10–12).

After a blind selection of articles by two authors (TC and AJS), data from each study were extracted by one author (TC, AJS, or OE), verified by a second author (TC, AJS, or OE), and summarised descriptively (appendix pp 10–12). We included research papers of original studies with: (1) definition of LLV consistent with persistent LLV (ie, repeated or sustained HIV-1 RNA measurements within the range of 50–1000 copies per mL, according to study-specific definitions), excluding studies focusing on residual viraemia or viral blips without a separate analysis of such LLV; (2) clinical data from adults on combined ART about factors predicting LLV, compartmentalisation during LLV, HIV drug resistance during LLV, subsequent virological, immunological and clinical outcomes, or interventions required during LLV; and (3) at least one comparator group, except for studies on compartmentalisation and drug resistance (appendix pp 10–12).

The key topics to be addressed by the consensus were identified by a writing committee in October 2023, informed by the scoping review and preliminary expert discussions.

Consensus process

84 papers met our inclusion criteria (appendix pp 16–29). The consensus process was informed by the data obtained by the scoping review and was conducted and reported in accordance with the ACCORD guideline (appendix pp 13–15).

International key opinion leaders were invited to participate in the consensus panel based on their expertise in HIV clinical management and research, including members of the European Society for Translational Antiviral Research board and council, and additional global experts identified through previous collaboration, discussion arising from the presentation of the project at the European AIDS Clinical Society 2023 conference, or from direct engagement with the core working group (appendix pp 10–12).

A questionnaire about key concerns regarding LLV stratified by viral load (50–200 and 200–1000 copies per mL) and by regimen genetic barrier was circulated to experts for their votes and comments. The regimen barrier questions initially covered multiple regimen categories and were subsequently grouped into high genetic barrier (including a boosted protease inhibitor, dolutegravir or bictegravir) versus low genetic barrier (all other cases, including long-acting cabotegravir–rilpivirine), based on panel responses from the first round and core working group consensus. A modified two-round Delphi process was used, consisting of an initial exploratory round followed by a formal consensus round. The first round was used to refine and restructure the statements based on panel feedback, and consensus was formally assessed in the second round. The process was developed through discussions held during an in-person meeting in conjunction with the 2023 European AIDS Clinical Society conference and subsequently refined by the core working group. In the first round, panellists completed an online survey that included structured questions and free-text responses. Responses were summarised quantitatively and qualitatively and used to inform the development of final statements. In the second round, panellists were asked to indicate agreement (yes or no) with each statement. Consensus was defined a priori as at least 70% agreement among panellists. 90% and above agreement was considered very high agreement.

The recommendations by the consensus panel incorporate a rating scheme based on the modified GRADE system. The strength of recommendation for each statement is indicated by grade 1 (strong) or 2 (weak). The quality of evidence for each recommendation is indicated as grade A–D, where A is high-quality evidence, B is moderate-quality evidence, C is low-quality evidence, and D is very low-quality evidence (appendix pp 10–12). The final document was approved by all panel members through a final voting process.

Definitions and outcomes

A definition of LLV was provided in all included studies (appendix pp 30–31), with the exception of seven case reports or case series. 69 (91%) of 76 studies defined LLV using a lower threshold of 50 copies per mL, whereas seven (9%) studies applied alternative lower thresholds (figure 2). 47 (62%) of 76 studies of studies used an upper limit of 1000 copies per mL (figure 2) that was consistent with thresholds historically applied and incorporated in LMIC guidelines for virological failure.[8] Of the remaining 29 studies, 18 (24%) studies used a threshold of 200 copies per mL, three (4%) studies used a threshold of 400 copies per mL, and eight (10%) studies used a threshold of 500 copies per mL (figure 2 and appendix pp 30–31). However, in guidelines from HICs, values of at least 200 copies per mL are generally classified as virological failure.[7,9,10]

Across all studies, 20 observational investigations evaluated the impact of LLV on virological failure (appendix pp 32–36) with heterogeneous definitions of virological failure, and commonly used a threshold of over 1000 copies per mL, in line with the historical use and incorporation of this threshold into current LMIC guidelines.[8]

An overview of LLV strata and their association with virological failure is given in table 1.[1–6,25–38] Of the nine studies that used a virological failure threshold of 1000 copies per mL, all found a statistically significant association between persistent LLV at 50–1000 copies per mL and subsequent failure.[1,2,6,27,28,32–34,37] However, all five studies[27,28,32–34] with sub-analyses by LLV stratum reported a statistically significant association between

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See **Online** for appendix

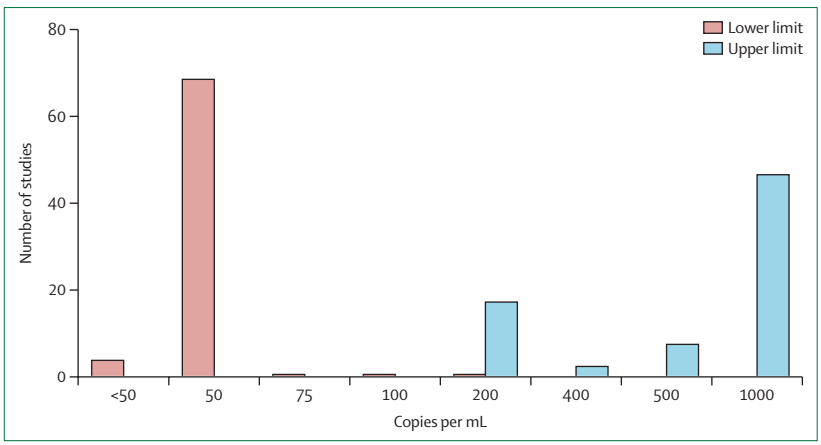

Figure 2: **LLV definition**
The number of studies that used a viral load (in copies per mL) for the lower threshold of the LLV definition and the number of studies that used a viral load (in copies per mL) for the upper threshold of the LLV definition (blue; right). Studies that used a lower definition of viral load of less than 50 copies per mL (residual viraemia) could only be included when a sub-analysis was possible within our inclusion range (50–1000 copies per mL). LLV=low-level viraemia.

	Association with virological failure	No association with virological failure
50–200 copies per mL	Virological failure of >200 copies per mL;[4,25] >500 copies per mL;[3,26] >1000 copies per mL;[27,28] and virological failure definition at different levels[5,29,30]	Virological failure of >500 copies per mL;[31] and >1000 copies per mL[32–34]
50–400 copies per mL	Virological failure of >400 copies per mL[35]	Virological failure of >400 copies per mL[36]
50–1000 copies per mL	Virological failure of >1000 copies per mL[1,2,6,37] and definition at different levels[38]	..
200–400 copies per mL	Virological failure of >1000 copies per mL[27]	..
200–500 copies per mL	Virological failure of >500 copies per mL[3,26,31] and >1000 copies per mL[28,32,33]	..
200–1000 copies per mL	Virological failure of >1000 copies per mL[34] and definition at different levels[30]	..
400–1000 copies per mL	Virological failure of >1000 copies per mL[27]	..
500–1000 copies per mL	Virological failure of >1000 copies per mL [28,32,33]	..

An overview of different studies with a suppressed control group that included an LLV stratum in their analysis for association with virological failure. Most studies found associations with virological failure. Note that different thresholds for virological failure are used in the association with and no association with virological failure columns. See appendix for further details on effect size and 95% CI (pp 32–36). LLV=low-level viraemia.

Table 1: **Association of different LLV strata with virological failure**

LLV of 200–1000 copies per mL and subsequent virological failure at 1000 copies per mL, with only two of these five studies showing a statistically significant association between LLV of 50–200 copies per mL and the same outcome. Thus, the absence of association in some studies was limited to the lower LLV stratum, and the association for LLV of 200–1000 copies per mL was consistent across studies. Nevertheless, this difference might partly reflect insufficient statistical power in analyses of the 50–200 copies per mL stratum, rather than a true absence of effect. When lower virological failure cutoffs (typically 200–500 copies per mL) were applied, findings remained consistent.

Clinical outcomes were evaluated in 11 studies, including nine cohort studies, one randomised controlled trial (RCT), and one case–control study (appendix pp 37–39).

Three studies evaluated all-cause mortality. One study reported a statistically significant increase in mortality among people with LLV of 50–1000 copies per mL,[39] including in a sub-analysis restricted to 50–200 copies per mL. The other two studies (one using a 50–1000 copies per mL threshold and one using a 50–200 copies per mL threshold) did not.[34,40] Two additional studies evaluated a composite endpoint of AIDS events and death, with one study finding a statistically significant association at LLV of 200–500 copies per mL but not at 50–200 copies per mL.[31] The other study did not find any such association for either range.[3]

Similarly, non-AIDS events (typically defined as a composite endpoint of multiple outcomes; eg, cardiovascular events, non-AIDS malignancies, liver disease, and chronic kidney disease) were investigated in four studies. Of these four studies, two studies found a statistically significant association of LLV of 50–200 copies per mL and 200–1000 copies per mL with an increased risk of non-AIDS events,[32,41] one study confirmed this association only for the 200–1000 copies per mL range,[39] and one study found no association.[31] No relationship was found with invasive cancer during a median follow-up of 5·3 years[42] or, separately, with cardiovascular disease during a median follow-up of 5·5 years.[43]

Predictive factors of LLV

Overall, two RCTs and 22 observational studies analysed the factors associated with persistent LLV (appendix pp 40–43). In the BENCHMRK trials, a rapid virological response to regimens that contained raltegravir in people who were heavily treatment-experienced was inversely associated with subsequent LLV, whereas pre-raltegravir immunovirological characteristics or resistance profile showed no association.[36] By contrast, the ACTG trials identified predictors of LLV, including type of anchor drugs (specifically protease inhibitors), high pre-treatment viraemia, and low pre-treatment CD4 cell count, but not demographic characteristics and adherence.[44]

15 observational studies investigated whether viraemia dynamics could predict persistent LLV, with ten studies finding an association between highest viraemia, pre-ART viraemia or viraemia preceding the onset of LLV, and subsequent persistent viraemia. One study showed an association between previous viral blips and

persistent LLV,[45] and another study found a relationship between previous residual viraemia and persistent LLV.[38] Similarly, among 18 investigations on the effect of immunological characteristics on LLV, nine studies identified lowest, pre-ART, or pre-LLV CD4 T-cell count as a predictor of persistent LLV. Of the five studies that investigated the role of adherence, only two studies found adherence to be a statistically significant predictor of LLV.[46,47] Two studies evaluated plasma drug levels as predictors of LLV,[48,49] but neither study found an association. Further details and other investigated risk factors for LLV are given in the appendix (pp 40–43).

Genotypic resistance testing during LLV

27 studies explored the detection of resistance-associated mutations during episodes of persistent LLV during ART, including two RCTs, one pre-planned analysis within a trial, 18 observational studies, and six case reports or series (appendix pp 44–48).

Resistance-associated mutations have been identified during LLV, even when HIV load is less than 200 copies per mL. However, the success rate of RNA-based genotypic resistance testing increases with higher HIV loads,[50–52] which is when the probability of detecting resistance-associated mutations is also greater.[51–54] Additionally, accuracy could be a concern when testing at low viral loads (less than 400 copies per mL),[50] as amplification might capture only a part of the viral population and might not reliably detect recently selected variants. In the absence of a standardised approach, some laboratories have implemented strategies to improve the yield of RNA-based genotypic resistance testing at low viral loads,[50] including increasing input volume and analysing multiple amplicons. Evidence on DNA-based genotypic resistance testing during LLV is poor: although DNA-based testing might have higher success rates than RNA-based genotypic resistance testing, the only comparative study reported a concordance of 75%.[55] Furthermore, data are scarce regarding the clinical use of DNA-based testing in guiding treatment decisions during LLV, particularly given the potential detection of defective, non-replication-competent proviruses from the reservoir, which might not fully represent the viral population underlying plasma viraemia.

Viral evolution (based on phylogenetic analysis) appears more pronounced in people with resistance-associated mutations detected during LLV compared with people without resistance-associated mutations, and is associated with increasing viral loads.[56] The spectrum of mutations is highly heterogeneous and depends on current regimens and treatment history, with specific mutations depending on current regimens and treatment history and potentially emerging during or before LLV episodes (appendix pp 44–48). The occurrence of resistance-associated mutations during LLV—although occasionally reported with high genetic barrier regimens—has been more frequently observed with low genetic barrier regimens (appendix pp 44–48), reflecting ongoing viral replication that might precede high-level virological failure (appendix pp 32–36).[32,44,52,57] However, it should be acknowledged that apolipoprotein B mRNA editing enzyme, catalytic polypeptide (APOBEC)-mediated hypermutation, which is more commonly identified in HIV-1 DNA and typically reflects defective proviruses, can occasionally be detected in HIV-1 RNA in the context of LLV.[17] In such cases, this detection might indicate that viraemia originates from defective proviruses rather than ongoing viral replication, and could help contextualise the risk of viral evolution, resistance accumulation, and virological failure.

Immunological assessment during LLV

Overall, 13 studies on immunological outcomes were included, which assessed CD4 T cell counts, CD4 and CD8 ratios, and soluble and cellular immune markers. Despite applying different LLV thresholds, five (83·3%) of six studies reported no negative impact on CD4 T cell counts,[36,44,49,58,59] and only one study observed lower CD4 levels in people with LLV of 50–1000 copies per mL compared with people without LLV (appendix pp 49–50).[60]

Six small studies investigated other immune variables, with each study including no more than 34 people with LLV. Three studies that used a LLV definition of 50–1000 copies per mL found no differences in the immune markers that were assessed.[17,38,61] One study with the same threshold reported an association with transcriptomic activity.[62] Two studies (one using a 50–1000 copies per mL threshold and one using a 50–200 copies per mL threshold) observed increased levels of activated HLA-DR, CD38, CD4, and CD8 T cells and higher senescence markers (eg, PD-1 and HAVCR2) in people with LLV compared with people on virological suppression.[63,64]

Compartmentalisation, reservoirs, and LLV

Overall, 13 studies investigated the relationship of LLV with HIV compartments or HIV reservoir. Eight studies focused on CNS compartmentalisation, one study focused on oral cavities as potential reservoirs, and four studies focused on the role of peripheral blood mononuclear cell reservoirs. Other potential reservoir compartments have not been investigated (appendix pp 51–53).

In people with LLV and neurological, neuropsychiatric, or neurocognitive symptoms, replication in the CNS as a source of viraemia in plasma should be considered, as shown by six case reports and two case series. Plasma viral load showed wide variation between 50 and 1000 copies per mL, and was seen both in the 50–200 copies per mL and in the 200–1000 copies per mL range. Cerebrospinal fluid viral load was frequently higher than 1000 copies per mL (appendix pp 51–53). Across these eight reports, a CD4 nadir was commonly described; however, the small number of available cases and heterogeneity of the reported data precluded the identification of a precise threshold.

Treatment switch during LLV

In total, nine studies reported virological suppression as an outcome (appendix pp 54–55): six with a control group (two RCTs, one case–control study, and three cohort studies) and three without a control group for this analysis. The SESOTHO trial was the only RCT that directly compared virological suppression according to ART switch, showing a clear increase in suppression to less than 50 copies per mL after switching from a non-nucleoside reverse transcriptase inhibitor-based regimen to a boosted protease inhibitor-based regimen during LLV of 100–1000 copies per mL.[65] The BENCHMRK trials provided data on LLV subgroups, but were not designed as LLV-switch trials, and did not include a comparison of suppression rates among people with LLV between study arms.[36] Finally, three of four retrospective studies reported higher suppression rates following regimen modification compared with no ART changes.[49,66–68]

In addition, three studies specifically assessed virological failure as the outcome and reported a decrease in virological failure risk following treatment switch (appendix pp 32–36).

Risk of transmission during LLV

A 2023 WHO systematic review defined LLV as 50–1000 copies per mL, and concluded that the risk of HIV transmission is negligible.[20] However, it should be noted that this systematic review focused exclusively on sexual transmission, excluded case reports and case series, and often grouped people with LLV with people who were virologically suppressed, making it difficult to determine the precise number of LLV cases analysed. Although large prospective studies have clearly shown the zero risk of sexual transmission at a viral load of less than 200 copies per mL, limitations of the WHO review might have led to an underestimation of the actual transmission risk at viral loads of 200–1000 copies per mL (only two transmission cases with viral load of more than 600 copies per mL were highlighted). No data were provided on other transmission routes (such as vertical or parenteral), precluding firm conclusions regarding transmission risk in these settings.

Consensus results and recommendations

Of 133 invited experts, 99 agreed to participate and 96 completed the first-round survey. These participants and eight additional members of the core working group constituted the final panel, which included clinicians, virologists, and researchers from multiple geographical regions (appendix pp 10–12). Of these final panel participants, 63 contributed to the second round.

The first round was conducted in November, 2023, and the second round was conducted in December, 2025. The first round was exploratory and informed the refinement and restructuring of the statements. Based on quantitative responses and qualitative feedback, the writing committee developed a final set of 18 statements for the second round. Several items were refined between rounds, including the grouping of ART regimens into high and low genetic barrier based on first-round responses (appendix pp 10–12).

In the second round, all statements reached the prespecified threshold for consensus (at least 70% agreement), with five reaching very high agreement (at least 90% agreement). Agreement across statements ranged from 74·6% to 98·4% (panel). No statements failed to reach consensus. The complete set of individual recommendations can be found in the panel. A schematic overview of these recommendations is also given as a decision tree (figure 3).

Discussion

HIV LLV during ART represents a global challenge in HIV care and, although not shown in all studies, is associated with adverse clinical and virological outcomes. However, differences in its definition and management still exist.

The need for internationally harmonised, evidence-based, and context-sensitive guidance is increasingly urgent, particularly in LMICs, where LLV can still receive limited clinical attention due to difficult access to care, restricted diagnostic capacity, virological failure thresholds set at 1000 or more copies per mL, and fewer treatment options. Without appropriate monitoring and intervention (when necessary), LLV can lead to virological failure and disease progression, drive the emergence of drug resistance, and compromise the long-term effectiveness of ART, ultimately threatening progress towards global HIV targets.

This International Consensus Group on Clinical Management of Low-Level Viremia offers evidence-based and expert-driven recommendations to address this need. This guidance summarises the available research on the clinical management of LLV during ART across diverse settings, with LLV defined as multiple viral loads between 50 and 1000 copies per mL. A major point of discussion is which definition for LLV is most accurate. In most instances in HICs, a LLV definition of consecutive viral load between 50 and 200 copies per mL is preferred. However, non-suppressible viraemia can also occur within the range of 200–1000 copies per mL, which does not always reflect or predict failure.[18] Moreover, in LMICs, a definition of consecutive viral load between 50 and 1000 copies per mL is more in line with current WHO guidelines and takes practical considerations into account. However, increasing evidence that supports the prognostic relevance of viral loads of at least 200 copies per mL might prompt future discussions on harmonising definitions of virological failure and LLV across settings.

To our knowledge, this scoping review represents the most comprehensive effort to date to consolidate evidence on LLV. This scoping review was conducted using a rigorous and transparent methodology,

Panel: **Consensus panel recommendations**

Definitions and outcomes

- Viral load between 50 and 200 copies per mL should raise initial concern (C2). The clinical significance of viral load might vary depending on several background factors (including stage of HIV disease, resistance barrier of the antiretroviral regimen, history of virological failure, drug resistance, and possible origin from clonal expansion) (D2). In contrast, viral load between 200 and 1000 copies per mL should be considered more concerning (B1) and, when confirmed, is generally used to define virological failure (C2; 92·1% agreement).
- Accordingly, any single measurement of viraemia between 50 and 1000 copies per mL should be repeated in a timely manner (eg, within 1 month; D1). In cases of viraemia between 50 and 200 copies per mL, repeat testing could be deferred (eg, within 3 months) in people receiving high-genetic barrier regimens who do not have a history of resistance to current antiretrovirals (D2; 84·1% agreement).
- In cases of persistent LLV, a comprehensive review of the ART history should be performed, considering historical viraemia and CD4 count dynamics, episodes of virological failure and resistance, previous regimens, current adherence, and potential interactions with other drugs, food, herbs, or medicinal preparations (C1; 93·7% agreement).

Predictive factors of LLV

- As persistent LLV might be caused by suboptimal adherence, any intervention should be preceded by adherence counselling (C1). Practical measures (eg, directly observed therapy) might also be considered (D2; 93·7% agreement).
- If available, drug exposure testing (to verify drug presence in plasma or urine) could be considered, especially in some situations (eg, pregnancy or suspected malabsorption) and at viral load of at least 200 copies per mL (D2; 79·4% agreement).

Genotypic resistance testing during LLV

- Resistance testing is advised at confirmation of LLV above 200 copies per mL if a validated assay is available (B2), and could be considered at confirmation of LLV between 50 and 200 copies per mL, particularly in people on low-genetic barrier regimens (C2; 81·0% agreement).
- RNA-based genotypic resistance testing and detection of resistance-associated mutations are technically feasible at viral loads of less than 200 copies per mL; however, successful sequencing and resistance identification are more likely at more than 200 copies per mL (B2). Treating physicians should provide the virology laboratory performing genotypic resistance testing with the viraemia value when requesting testing at HIV loads of less than 1000 copies per mL (D2; 84·1% agreement).
- When performing resistance testing during LLV, plasma volume could be increased—providing that the assay is validated—allowing the laboratory to concentrate the samples (D2; 88·9% agreement).

Immunological assessment during LLV

- CD4 T-cell count testing (and CD4 or CD8 ratio, if available) is advised at least once in people with LLV that has persisted for at least 3–6 months (D2; 88·9% agreement).

Compartmentalisation, reservoirs, and LLV

- In people with persistent LLV—especially those with a low CD4 nadir—potential CNS viral escape and compartmentalised viral evolution should be considered (D2; 74·6% agreement).
- In people with persistent LLV and neurological symptoms and signs of unknown aetiology, CNS compartmentalisation and cerebrospinal fluid viral escape should be assessed by measuring viral load on cerebrospinal fluid after brain imaging (D2; 84·1% agreement).

Treatment switch during LLV

- In the absence of newly emergent resistance-associated mutations or in the absence of results from RNA-based genotypic resistance testing, current ART can be continued if a high-genetic barrier regimen is used (or the regimen has been constructed for people with limited treatment options), especially for viral loads between 50 and 200 copies per mL (D2). Switching from low-genetic barrier regimens to high genetic barrier regimens should be considered, even if no resistance is detected (C2; 87·3% agreement).
- If resistance-associated mutations are detected by RNA-based genotypic resistance testing during persistent low-level viraemia, ART should be modified, with the type of mutations, predicted antiretroviral susceptibility, previous treatment history, and remaining treatment options considered (D1; 98·4% agreement).
- If only de novo M184I/V mutation is detected when a person is on a regimen that contains emtricitabine or lamivudine, ART modification should be considered, especially in the case of low-genetic barrier and dual emtricitabine or lamivudine-based therapies (D1). If NRTIs are included in the new regimen, keeping emtricitabine or lamivudine as part of a triple therapy should be considered, as M184I/V could prevent the selection of other NRTI mutations (D2; 88·9% agreement).

(Panel continues on next page)

including multiple iterative discussions within the core working group and validation by a broader international panel. This is the first multiregional initiative specifically dedicated to LLV, involving experts from a wide range of clinical and geographical backgrounds. Although several limitations exist, these shortcomings largely reflect the current state of the evidence base. The studies included in this scoping review varied in design,

(Continued from previous page)

- In people who remain on their current regimen during LLV, viral load testing should be performed more frequently than regular follow-up (eg, every 3–4 months), at least within the first year (D1; 90·5 % agreement).
- In people who switched to a new regimen during LLV and do not reach virological suppression (HIV load of less than 50 copies per mL) within 6 months, repeating genotypic resistance testing could be considered (D2; 82·5 % agreement).
- If good adherence to ART is documented and no emergent resistance-associated mutations are detected, persistent LLV might indicate non-suppressible viraemia, which could result from the production of defective viruses or from replication-competent viruses that are unable to complete their replication cycles (D2). Although rare, detection of APOBEC3-related mutations on RNA-based genotypic resistance testing could support the hypothesis of defective viral production (D2; 88·9% agreement).

Risk of transmission during LLV

- No sexual transmission of HIV has been documented with LLV values of 50–600 copies per mL. However, additional strategies to prevent the sexual transmission of HIV (eg, condom use, PrEP for partners) should be considered when viral load is between 200 and 1000 copies per mL, taking into account individual risk factors, the potential for active viral replication, and the variable dynamics of viraemia, including fluctuations over time and the potential for upward trends (B1; 79·4% agreement).

The percentage of agreement on consensus statements in the second Delphi round by the International Consensus Group on Clinical Management of LLV is given after each point in parenthesis. The recommendations by the consensus panel incorporate a rating scheme based on the modified GRADE system that is included after each statement, where the strength of recommendation for each statement is indicated by grade 1 (strong) or 2 (weak). The quality of evidence for each recommendation is indicated as grade A–D, where A is high-quality evidence, B is moderate-quality evidence, C is low-quality evidence, and D is very low-quality evidence. ART=antiretroviral therapy. LLV=low-level viraemia. NRTI=nucleoside reverse transcriptase inhibitor.

definition of LLV, and outcome measures, which limits comparability. Within individual studies, stratification was often based on the highest viral load recorded, potentially overlooking episodes of LLV at 50–200 copies per mL when people were classified according to a higher viral load category. This methodological approach, together with the heterogeneity in LLV definitions, could have influenced the interpretation of risk across strata, contributing to the less consistent associations observed for the 50–200 copies per mL range. The low representation of studies from LMICs could also reduce the generalisability of these findings and the applicability of recommendations in settings where the clinical burden is greatest, but diagnostic capacity and treatment options are constrained. A formal study-level critical appraisal was not conducted, as the aim was to provide a broad overview of the global evidence base and inform practical recommendations, rather than a systematic evaluation. In addition, the consensus process itself has limitations, including potential selection bias in panel composition, unequal geographical representation, and reduced participation in the second Delphi round, which could have influenced the results. In light of these limitations, a structured and actionable research agenda is required. Priority areas include prospective studies with standardised and time-updated definitions of LLV; mechanistic investigations to distinguish replicative from non-replicative viraemia; and interventional and implementation studies to guide management strategies across diverse settings, particularly in LMICs. These priorities, along with recommended study designs and their anticipated clinical impact, are given in table 2.

Key recommendations apply differently across viral load strata and should distinguish between the management of persistent LLV at 50–200 copies per mL and at 200–1000 copies per mL. In all cases, viral load testing should be repeated promptly after the initial detection of LLV, with frequency tailored to viraemia level and regimen genetic barrier. Adherence assessments and reviews of potential drug–drug or drug–food interactions should precede any intervention, and drug exposure testing can be considered in specific conditions and when available, although evidence linking drug levels to LLV remains sparse and represents a key knowledge gap. Moreover, although poor adherence is a recognised driver of LLV in clinical practice, this association has not been observed in trials[44] and possibly reflects structured adherence support in those contexts, which is not always replicated in routine clinical care. Despite its potential limitations, RNA-based genotypic resistance testing should be considered with persistent LLV of 50–200 copies per mL, and is strongly advised for persistent LLV between 200–1000 copies per mL, if a validated assay is available. Conversely, further studies are needed to clarify the potential role of DNA-based genotypic resistance testing in this setting, and consensus was reached to consider this a knowledge gap (table 2), as the interpretability of results might be limited by APOBEC3G-introduced hypermutations and the presence of a high frequency of defective genomes in proviral DNA without clear implications for ongoing viraemia.[69] Such approaches are frequently included in HIC guidelines, but often missing from LMICs,[7–11] contributing to disparities in care. A broader clinical investigation, including a thorough evaluation of neurological signs that suggest CNS HIV replication and CD4 T cell assessments, is recommended. Despite acknowledging that cerebrospinal fluid escape is rare with modern second-generation integrase strand

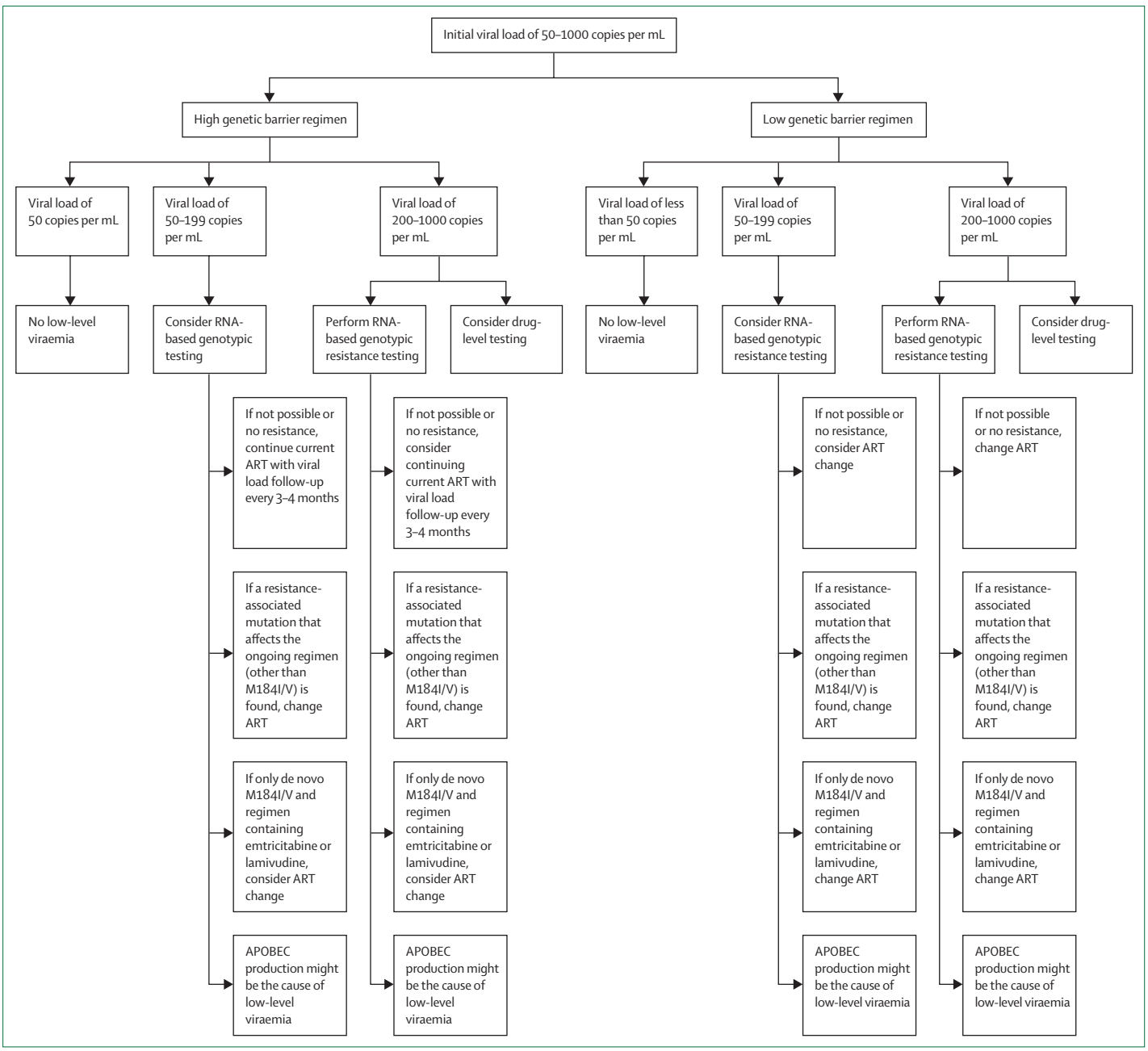

Figure 3: **LLV decision tree**
Before any intervention, adherence assessments and checks for drug–drug interactions should be completed. If LLV persists for 3–6 months, it is advised to perform CD4 T cell count testing (and CD4 or CD8 ratio, if available) at least once. Potential CNS viral escape should be also considered and—if neurological symptoms and signs of unknown aetiology are present—viral load should be measured in cerebrospinal fluid. If LLV persists for 6 months after an ART change, repeat genotypic resistance testing should be considered, as LLV might be non-suppressible viraemia. High genetic barrier regimens are regimens that contain a high genetic barrier drug (eg, dolutegravir, bictegravir, or boosted darunavir). Low genetic barrier regimens are regimens that do not contain a high genetic barrier drug. APOBEC=apolipoprotein B mRNA editing enzyme, catalytic polypeptide. ART=antiretroviral therapy. LLV=low-level viraemia.

transfer inhibitor-based regimens,[70] and despite overall reassuring evidence on CD4 count, these elements (currently missing in most guidelines)[7–10] might help to exclude potential individual-level alterations in the context of weak and heterogenous available data. No specific recommendations were made on screening for non-AIDS comorbidities in the setting of LLV, due to scarce and inconsistent evidence.

Therapeutic guidance is based on genotypic resistance testing results, viral load strata, and regimen genetic barrier. Given its increasing use in simplification strategies, long-acting cabotegravir–rilpivirine is included among

	Preferred type of study and evidence	Clinical impact
What monitoring strategies (eg, optimal frequency of viral load measurements) and interventions (pharmacological and non-pharmacological) most effectively prevent virological failure and resistance development in people with LLV?	Randomised controlled trial	Support evidence-based decision-making when and how to apply or withhold interventions during LLV; this knowledge gap is likely context dependent and should also be applied to LMICs
Does proviral DNA resistance testing during LLV change clinical management and improve virological outcomes (suppression and prevention of failure), and in which populations or treatment contexts?	Randomised controlled trial	Clarify the predictive value and clinical use of DNA genotypic resistance testing during LLV, and whether and when it should be requested
Which feasible diagnostic methods can be applied to distinguish replication-driven LLV from clonal production, and do these methods predict benefit from regimen change?	Assay development and validation study	Provide a clinically applicable diagnostic tool to guide whether a change of regimen is indicated
In dolutegravir or bictegravir-based ART, what is the virological failure risk associated with LLV per viral load stratum and duration of LLV?	Cohort study	Provide accurate risk estimates of virological failure subsequent to LLV in people on second generation integrase inhibitor-based regimens; this knowledge gap is likely context dependent and should also be applied to LMICs
What is the clinical and immunological significance of LLV attributable to defective genomes versus replication-competent virus?	Cohort study	Improve risk stratification of LLV and inform the need for additional interventions
What is the psychological and behavioural impact of LLV?	Observational study	Improve counselling, adherence support, and shared decision-making, and maintain confidence in treatment effectiveness and prevention of transmission; this knowledge gap is likely context dependent and should also be applied to LMICs
Can quantification of the HIV-1 reservoir predict the risk of persistent LLV?	Cohort study	If quantification of the DNA reservoir can predict the risk to develop LLV this can help in informed decision making (eg, identify people who might benefit from more frequent monitoring or identify those at higher risk for non-suppressible viraemia)

LLV=low-level viraemia. LMIC=low-income and middle-income country.

Table 2: **Knowledge gaps**

low-to-medium genetic barrier regimens. Although few published data are available on LLV in people receiving long-acting cabotegravir–rilpivrine, this clinical scenario represents an area of growing clinical and research interest, particularly as emerging evidence suggests that LLV might occur even with confirmed adherence, supporting the contribution of mechanisms beyond adherence.[44,49,71,72] In addition to cases where new major resistance-associated mutations are detected and where this guidance aligns with existing recommendations,[7–10] we propose a stepwise management approach for scenarios where resistance testing is unavailable or yields no major mutations, including considering switching from low to medium genetic barrier regimens and implementing closer monitoring. The consensus group further acknowledges that LLV could sometimes reflect non-suppressible and non-infectious viral production from the reservoir and might not require ART changes, although distinguishing this from replicative LLV in standard care remains challenging and warrants further investigation.[15] These considerations also highlight the importance of clear communication with people engaged in HIV care about the potential mechanisms underlying LLV, addressing existing uncertainties and possible clinical implications to support shared decision making.

In summary, LLV is an important and under-recognised occurrence that threatens ART durability and contributes to virological failure and resistance. This international guidance offers an evidence-based and pragmatic framework to support HIV care providers managing LLV in diverse settings and reduce unwarranted variability in practice. However, considerable gaps remain, particularly in access to diagnostics, harmonised monitoring strategies, and clarity on when intervention is required (table 2). Continued investment in implementation research and equitable access to diagnostics and care will be essential to refine LLV management. Ultimately, addressing LLV represents a crucial step toward sustaining treatment success and advancing progress toward global HIV control targets.

Contributors

TC and AJS conceptualised and drafted the manuscript and performed data curation and formal analysis. TC acquired funding for this project. OE performed data curation and formal analysis and drafted the manuscript. AMG, RH, MP, NEM, VS, MH, FV, DRK, JML, RWS, JS, EM, CK-M, MN, PB, CC, SC, HFG, DC, and AC supervised and drafted the manuscript. NB contributed to developing the study methodology and supervised and drafted the manuscript. AMJW conceptualised, supervised, and drafted the manuscript.

Declaration of interests

TC received funding from the European AIDS Clinical society for a Career Development Fellowship related to this work; and received

personal fees for speaker panels and travel grants from Gilead Sciences and ViiV Healthcare. OE received payments to his institution for speaker panels by Gilead Sciences. AMG received payments to her institution for grants by Gilead Sciences, ViiV Healthcare, and Roche; received travel grants from ViiV Healthcare; received experimental equipment by Gilead Sciences and Roche; received consultancy fees from Gilead Sciences, ViiV Healthcare, and MDM Medical; received personal fees for speaker panels from Gilead Sciences, ViiV Healthcare, MSD, and Roche; held a position on advisory boards for ViiV Healthcare and MSD; holds stocks in Roche; is Editor-in-Chief of Sexually Transmitted Infections (*BMJ* Group, honoraria paid to her and her institution); and is an unpaid member of the British HIV Associations guidelines committee. MP received personal fees for speaker panels from Gilead Sciences, ViiV Healthcare and GSK, Janssen, Pfizer, MSD, and Abbvie. NEM received personal fees for participating in advisory boards from Gilead Sciences and ViiV Healthcare. VS received personal fees for speaker panels and travel grants from Gilead Sciences, ViiV Healthcare, and MSD. FV received payments to his institution for grants from the Gates Foundation, South African Medical Research Council, National Institutes for Health (NIH), Foundation for Innovative New Diagnostics, MSD, and the Children's Investment Fund Foundation; received financial support for conducting studies by MSD, Gilead Sciences, and Novo; received personal fees for speaker panels and advisory boards from ViiV Healthcare, Mylan and Viatris, MSD, Adcock-Ingram, Aspen, Abbott, Roche, Sanofi, Boehringer Ingelheim, Thermo Fisher, and Virology Education; and has previously participated on international data and safety monitoring boards for NIH. DRK received payments to his institution for grants by NIH; received personal fees for consultancies from Gilead Sciences, ViiV Healthcare, MSD, and Abbvie; received fees for expert testimony from Gilead Sciences and Jannsen; and has held a position on an advisory board for GSK. JML received personal fees for consultancies from MSD; received fees for speaker panels from Gilead Sciences and ViiV Healthcare; and has received travel grants from Gilead Sciences. JS received personal fees for speaker panels, advisory boards, and travel grants by Abbvie, MSD, Gilead Sciences, and GSK and ViiV Healthcare. EM received payments to his institution for grants from MSD, Gilead Sciences, and ViiV Healthcare; received personal fees for participating on advisory boards from MSD and ViiV Healthcare; and is a board member of the European AIDS Clinical Society and NEAT-ID. MN received payments to her institution for grants from ViiV Healthcare. PB received payments to his institution for national and regional grants from Swedish Governmental research grants and the Swedish Heart Lung Foundation; and received personal fees for speaker panels and advisory boards from Gilead Sciences and GSK. CC received personal fees for speaker panels and travel grants by Gilead Science, MSD, and ViiV Healthcare. HFG received payments to his institution for grants from the Swiss National Science Foundation, the Swiss HIV Cohort Study, Yvonne Jacob Foundation, Gilead Sciences, ViiV Healthcare, and the Gates Foundation; received consultancy fees from MSD; and held a position on advisory boards by Gilead Sciences, ViiV Healthcare, and MSD. AC received personal fees for advisory boards, speaker panels, and educational materials from Gilead Sciences, ViiV Healthcare, Janssen, MSD, and Theratechnlogies. AMJW received payments to her institution for grants from Gilead Sciences; received consultancy fees from ViiV Healthcare and GSK, Gilead Sciences, MSD, and Roche; and received experimental equipment from Ark. All other authors declare no competing interests.

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