Establishing shared definitions of virological failure and discontinuation for long-acting injectable cabotegravir and rilpivirine therapy (the CONSENSUS-LAI Study): an international survey and Delphi process

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Summary

Background Definitions of virological failure and treatment discontinuation for long-acting injectable (LAI) cabotegravir and rilpivirine antiretroviral therapy are inconsistent in clinical practice and observational studies, which complicates interpretation and implementation of findings. The CONSENSUS-LAI study aimed to establish consistent definitions of virological failure and treatment discontinuation to enhance evidence transferability and support optimal clinical outcomes.

Methods The study had two phases. Phase 1 was an international online survey exploring existing definitions of virological and treatment discontinuation, conducted between April 25 and July 1, 2024. Eligible participants were health-care professionals working in infectious disease or sexual health services who had provided care to at least ten people living with HIV in the past 6 months, had prescribed LAI cabotegravir and rilpivirine in clinical trials or clinical practice, and were able to give informed consent. Participants were recruited via social media and mailing lists of medical specialist societies. Phase 2 was a Delphi process, in which a panel of experts, selected to ensure representation from all six WHO regions, scored leading definitions from phase 1 on a 9-point Likert scale. The proposed definitions were scored according to four validity criteria: clarity, usability in the expert's setting, appropriateness across clinical purposes, and applicability across relevant population groups. Revisions were suggested in iterative rounds until consensus was reached. Consensus was predefined as at least 75% of experts agreeing or strongly agreeing (scores 7–9) with the validity criteria.

Findings 386 LAI cabotegravir and rilpivirine prescribers across 28 countries completed the survey, revealing 15 definitions for virological failure on LAI cabotegravir and rilpivirine and nine for treatment discontinuation. 52 experts participated in the Delphi process. Consensus agreement on both definitions was reached after two rounds for all validity criteria. For virological failure, the consensus definition was as follows: (a) viral load 200 copies or more per mL or more on two occasions 2–4 weeks apart, or (b) a single viral load of more than 1000 copies per mL, and/or (c) emergent resistance, in the context of timely injections and prior suppression of less than 200 copies per mL, OR (d) unable to suppress viral load to less than 200 copies per mL on continuous therapy. For treatment discontinuation the consensus definition was as follows: people on LAI cabotegravir and rilpivirine who have missed two consecutive injections and have not taken oral bridging in the interim, irrespective of reason for discontinuation.

Interpretation The consensus definitions provide a foundation for aligning practice and evaluating patient outcomes. Further validation of the viral load threshold for virological failure and the optimal viral load retesting window is required.

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Introduction

Randomised controlled trials (RCTs), implementation science, and observational studies of antiretroviral therapy involving long-acting injectable (LAI) cabotegravir and rilpivirine routinely report rates of virological failure as a core treatment outcome.[1–5] In RCTs of LAI cabotegravir and rilpivirine to date, virological failure is consistently defined as two consecutive viral loads of at least 200 copies per mL.[1–3] However, in clinical practice and observational

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Research in context

Evidence before this study

Long-acting injectable (LAI) cabotegravir and rilpivirine is licensed for use in people living with HIV-1 with viral suppression and is increasingly being recommended as a treatment option in high-income settings. This combination has been shown to be non-inferior to daily oral therapy in clinical trials, with low rates of confirmed virological failure (defined as two consecutive viral loads ≥200 copies per mL). However, when virological failure does occur on LAI cabotegravir and rilpivirine, resistance to both agents might occur. Literature on experience in clinical practice is growing with a substantial focus on descriptions of virological failure and emergence of resistance. However, virological failure and treatment discontinuation are often inconsistently or inadequately defined across this literature and, in some cases, the definitions used differ from those in randomised clinical trials. Additionally, in clinical practice, unlike in clinical trials, the frequency of HIV-RNA monitoring is highly variable and dependent on both clinical setting and engagement in care. We conducted a systematic review to describe the range and consistency of definitions used to report on virological failure outcomes in the context of observational studies of LAI cabotegravir and rilpivirine. We searched electronic databases (MEDLINE, PubMed, and Embase) with the key terms "long-acting injectable" AND "HIV" AND ("implementation study" OR "real-world study") with no language or date restrictions. We also hand-searched conference websites of 21 international and eight national conferences, which occurred between Jan 1, 2020, and Nov 30, 2023, for relevant abstracts and presentations. We included studies evaluating LAI cabotegravir and rilpivirine that were not randomised clinical trials and excluded case reports or series that included fewer than ten people and those without virological outcomes. We identified 39 observational studies across 13 countries and found that 15 (38%) studies described virological failure events but did not define virological failure in the methods. Among the 24 (62%) studies that provided a definition of virological failure, nine different definitions were used. Definitions included single and confirmed HIV RNA concentrations that exceeded specific numerical thresholds (eg, 50 or 200 copies per mL) and some incorporated treatment discontinuation into the virological failure definition. The wide variability and discrepancy in accepted definitions used for oral therapy highlights the challenge that clinicians face contextualising virological failure and treatment discontinuation in people receiving LAI cabotegravir and rilpivirine. To our knowledge, there have been no studies or initiatives from expert bodies to establish consensus definitions for virological failure and treatment discontinuation in the context of LAI cabotegravir and rilpivirine.

Added value of this study

Especially restrictive definitions cause unconfirmed blips to be considered as virological failure, which hinders a clear understanding of the risk of virological failure in clinical practice. Given the lower genetic barrier of LAI cabotegravir and rilpivirine, a consensus definition of virological failure in the context of this regimen is urgently needed. CONSENSUS-LAI (The Consensus on Long-Acting Injectable study) is the first study to explore definitions of virological failure and treatment discontinuation in the context of LAI cabotegravir and rilpivirine. We conducted an international survey and a Delphi process with global experts. The international survey revealed that 15 different definitions of virological failure and nine different definitions of treatment discontinuation are being used in analysing real-world data. The most common definition of virological failure (HIV viral load ≥200 copies per mL on two consecutive occasions) was used by only 203 of 386 (53%) respondents. The Delphi panel achieved early consensus that establishing shared definitions of virological failure and treatment discontinuation was feasible and important for optimal care. After two rounds of the Delphi process, consensus definitions for virological failure and for treatment discontinuation were achieved. The consensus definition of virological failure was: (a) HIV RNA of 200 copies per mL or more on two occasions 2–4 weeks apart, or (b) a single viral load of more than 1000 copies/mL, and/or (c) emergent resistance, in the context of timely injections and prior suppression of less than 200 copies/mL; OR (d) unable to suppress viral load to less than 200 copies/mL on continuous therapy. The consensus definition of treatment discontinuation was people on LAI cabotegravir and rilpivirine who have not received two consecutive injections and have not taken oral bridging in the interim, irrespective of reason for discontinuation.

Implications of all the available evidence

The consensus definitions of virological failure and treatment discontinuation reached in this study provide an opportunity for consistent reporting and classification of these important outcomes in both clinical and research settings. Use of these consensus definitions will provide clinicians with greater confidence in interpreting and comparing outcomes of LAI cabotegravir and rilpivirine in clinical care and observational cohorts. By providing standardised definitions for virological failure and treatment discontinuation, this consensus offers a foundation for greater alignment in the reporting of virological outcomes across settings. This foundation, in turn, might support efforts to harmonise global and national HIV treatment guidelines for LAI antiretroviral therapy by ensuring that policy recommendations are based on consistent and comparable virological endpoints. As the use of LAI cabotegravir and rilpivirine expands, standardised definitions will be essential for guiding treatment decisions, supporting clinical management, and facilitating regulatory and guideline development.

studies, definitions of virological failure vary widely across cohorts, which leads to inconsistencies in reported outcomes.[6–9] Although general guidelines for the use of LAI cabotegravir and rilpivirine exist,[10–13] there are currently no established guidelines specific to virological failure thresholds for these regimens, which contributes to variability in clinical practice and research reporting.

Observational studies reflect routine clinical practice. A recent systematic review[9] of early observational cohorts using LAI cabotegravir and rilpivirine revealed considerable and concerning variation in how virological failure is defined. In many instances, these definitions differed from those used in clinical trials.[6,14,15] The use of definitions that focus on single, unconfirmed viral load values is frequent.[15–18] Alternative definitions that include treatment discontinuation as an aspect of virological failure are being used in large observational cohorts.[6,19–22] This variation in definitions makes identifying and sharing of best practice from observational cohorts more challenging and might obscure important trends. This inconsistency might be due to concern on the part of health-care professionals regarding virological failure on LAI cabotegravir and rilpivirine, despite the non-inferior efficacy reported in RCTs, implementation science, and observational cohorts compared with oral therapy so far.[1–6,14–23] RCTs have shown that although virological failure with LAI cabotegravir and rilpivirine is rare, viral resistance has accompanied virological failure more commonly for individuals receiving this therapy than for those receiving modern oral integrase strand-transfer inhibitor-based regimens,[1–3,24] which has implications for subsequent regimen choice.

Unlike with oral regimens, long-acting treatment is not subject to fluctuations in adherence patterns, provided that the injections are administered correctly and on time, ensuring consistent drug exposure. However, pharmacokinetic differences in injectable therapies such as LAI cabotegravir and rilpivirine mean that drug concentrations can be measured at low plasma levels for more than a year, potentially leading to resistance. Therefore, establishing standardised definitions of treatment discontinuation that are specific to these unique LAIs is essential. This process is especially relevant as more long-acting regimens with extended half-lives are introduced.[25] Our study aimed to establish consensus definitions for virological failure and treatment discontinuation in the context of LAI cabotegravir and rilpivirine to enhance evidence transferability and support optimal clinical outcomes.

Methods

Study design

This study included two phases, with insights from phase 1 informing phase 2 (figure 1). The statistical analysis plan for both phases was developed before data collection and uploaded to Open Science Framework.

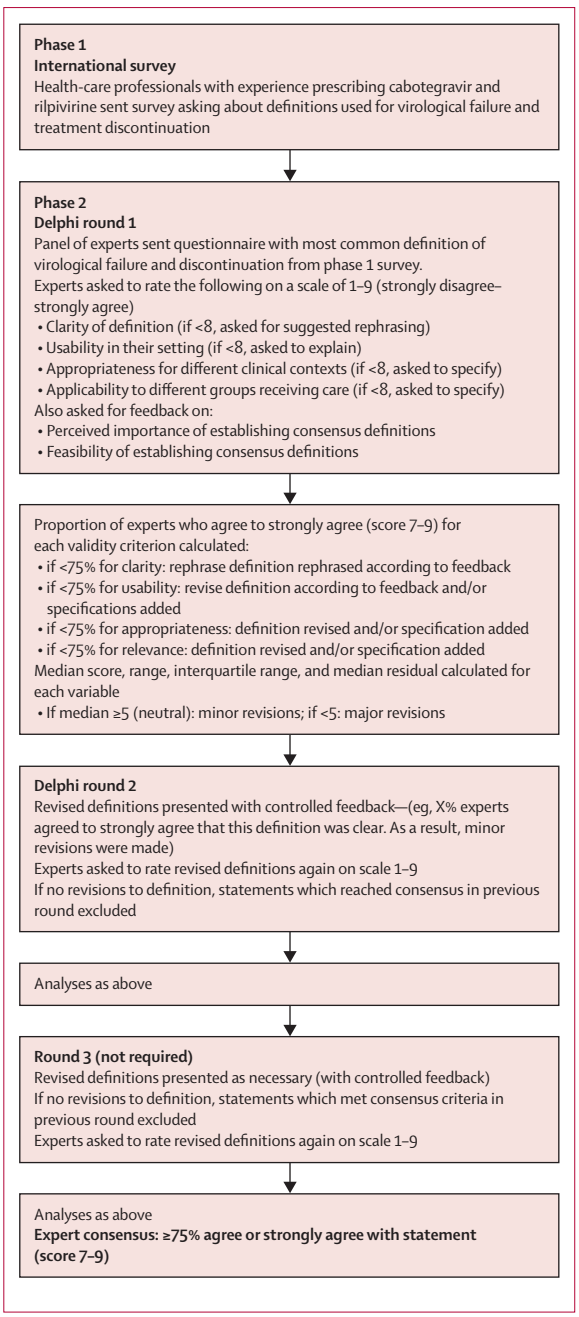

Figure 1: **Visual overview of study flow**

The study was approved by the Queen Mary University Ethics Board (reference QME24.0435). All participants provided voluntary informed electronic consent before participation, and their contributions were anonymised to protect confidentiality.

International survey

Phase 1 was an international survey exploring existing definitions of virological failure and treatment discontinuation used when prescribing LAI cabotegravir

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For more on the **statistical analysis plan** see https://doi.org/10.17605/OSF.IO/WK6PN

and rilpivirine therapy. The survey was conducted online between April 25 and July 1, 2024. Eligible participants were health-care professionals working in infectious disease or sexual health services who had provided care to at least ten people living with HIV in the past 6 months, had prescribed LAI cabotegravir and rilpivirine in clinical trials or clinical practice, and were able to give informed consent.

A target sample size of at least 150 participants was set to ensure a margin of error of less than 5%, calculated with the use of the Wilson Score method. To enhance representation across regional subgroups and low-income and middle-income countries (LMICs), participants were recruited not only from countries where LAI cabotegravir and rilpivirine is licensed, but also from those where it is not yet licensed but has been used in RCTs.

Participants were recruited via social media and mailing lists of medical specialist societies, including the British HIV Association, British Association for Sexual Health and HIV, European AIDS Clinical Society, HIV Medicine Association, Southern African HIV Clinicians Society, Canadian HIV Clinical Trials Network, and International AIDS Society. The survey included a mix of closed and open-ended questions covering respondent demographics, clinical experience, and definitions of virological failure and treatment discontinuation used for oral and LAI therapies.

Descriptive statistics (frequencies and percentages) of health-care professional characteristics (including gender identity, age, region, professional role, work setting, and experience in HIV management) and use of the various definitions of virological failure and treatment discontinuation were calculated with the use of STATA (version 18.0). Subgroup analyses were predefined in the statistical analysis plan and conducted when a subgroup sample was larger than 50 participants. Free-text responses were collated to understand the range of adopted definitions.

Delphi process

In phase 2, a Delphi process was used to develop consensus definitions for virological failure and treatment discontinuation in the context of LAI cabotegravir and rilpivirine therapy. The Delphi method is a structured technique designed to achieve consensus among experts through a series of questionnaire rounds that allow for controlled feedback and refinement of responses. This iterative process fosters reflection, explores tensions, and minimises the influence of dominant voices.[26] This Delphi process was done and reported following established Delphi methodological criteria,[27] which include clearly defining the study objective, selection criteria for panellists, predefined consensus criteria, and stopping criteria or maximum number of rounds.[27]

The expert Delphi panel consisted of a gender-balanced selection of health-care professionals with experience prescribing LAI cabotegravir and rilpivirine who also met the requirement of being HIV medical society leaders, national or international guideline developers, journal editors, conference organisers, or heads of division or department, and community representatives with lived experience. Experts were approached by email and selected to ensure representation from all six WHO regions (while recognising that there would be more eligible experts in regions where LAI cabotegravir and rilpivirine is licensed and available) and varying senior roles in the field (eg, HIV journal editors, heads of clinical departments, and policy makers).

The draft definitions for the Delphi process (phase 2) were derived from the most common definitions in phase 1. The definitions were: HIV viral load of more than 200 copies per mL on two consecutive occasions once viral suppression achieved for virological failure; and people who have missed one injection and are uncontactable irrespective of viral load for treatment discontinuation.

In round one of the Delphi process, experts provided demographic information and scored initial definitions of virological failure and treatment discontinuation for LAI cabotegravir and rilpivirine. The proposed definitions were scored according to four validity criteria: clarity; usability in the expert's setting; appropriateness across clinical purposes (including clinical trials, observational studies, and clinical care); and applicability across relevant population groups (irrespective of viral suppression at time of switch). Scoring was performed on a nine-point Likert scale from strongly disagree (1) to strongly agree (9). For scores of less than 8, experts were encouraged to provide detailed feedback and propose revisions, helping to clarify concerns and highlight areas of disagreement. The feasibility and importance of establishing consensus definitions were also scored with the use of the same Likert scale.

After each round, definitions were revised based on feedback. Definitions scoring a median of 5 or more were subject to minor revisions (rephrasing but no change in meaning), whereas definitions with scores of less than 5 underwent major revisions (including change in meaning). The revised definitions were presented back to the panel along with a summary of the previous round's scores and feedback. The panel then scored the revised definitions with the use of the same Likert scale. This process continued iteratively until consensus was achieved or a maximum of three rounds was completed.

Consensus was predefined as at least 75% of participants scoring the definition between 7 and 9 (agree to strongly agree) for each of the validity criteria, in line with previous Delphi studies using the same Likert scale.[28]

Descriptive statistics were used to summarise participant demographics (frequencies and percentages).

After each round, the proportion of experts who agreed or strongly agreed (scores 7–9) with each definition was calculated. Median scores and interquartile ranges were reported for each question.

Role of the funding source

The study sponsor reviewed the study design, statistical analysis plan, and manuscript. The study sponsors had no role in data collection. The decision to submit the manuscript was made independently by the authors.

Results

386 LAI cabotegravir and rilpivirine prescribers across 28 countries participated in the phase 1 international online survey (table 1). 300 (78%) respondents were hospital-based and 85 (22%) reported currently prescribing long-acting therapy to more than 50 people.

The survey revealed that there are 15 definitions of virological failure in current use for LAI cabotegravir and rilpivirine, and nine for treatment discontinuation. The most common definition of virological failure was an HIV viral load more than 200 copies per mL on two consecutive occasions (table 2). The most common definition of treatment discontinuation was patients who have missed one injection and are uncontactable irrespective of viral load (table 2). These remained the most common definitions across all regions, ages, experiences, and work setting subgroups analysed (appendix pp 2–5). An error in the branching logic in the survey meant that not all participants were given the opportunity to respond to the set of questions on discontinuation resulting in a response cliff prior to these questions.

Round 1 of the Delphi was completed by 52 experts (79% with >20 years of experience), including five community representatives, with representation from all six WHO regions (table 3). Panellists were residents of the following 21 countries: Argentina, Australia, Canada, Chile, Finland, France, Germany, India, Israel, Italy, Kenya, the Netherlands, Poland, Singapore, South Africa, Spain, Sweden, Switzerland, the UK, the USA, and Zambia.

In the first round there was consensus that shared definitions of virological failure and treatment discontinuation were important for care provision (94% agreement for virological failure [49 experts], 90% for treatment discontinuation [47 experts]) and feasible (89% for virological failure [46 experts], 87% for treatment discontinuation [45 experts]).

The initial virological failure definition (HIV viral load of more than 200 copies per mL on two consecutive occasions once viral suppression achieved) was, by consensus, considered clear and usable, but not appropriate across clinical purposes (including clinical trials, observational cohorts, and clinical care), or applicable across population groups (irrespective of viral suppression at time of switch; figure 2). These findings

	Number of respondents (%; N=386)
Region	
European	186 (48%)
Americas	141 (37%)
Western Pacific	45 (12%)
African	14 (4%)
Eastern Mediterranean	0
Age	
<45 years	340 (88%)
≥45 years	42 (11%)
Prefer not to say	4 (1%)
Self-identified sex	
Female	208 (54%)
Male	170 (44%)
Non-binary	2 (1%)
Other	1 (<1%)
Prefer not to say	5 (1%)
Staff group	
Specialist physician	301 (78%)
Trainee or junior doctor	24 (6%)
Pharmacist	24 (6%)
Nurse prescriber	19 (5%)
Senior nurse	9 (2%)
Physician assistant	8 (2%)
Junior nurse	1 (<1%)
Work setting	
Hospital—providing inpatient and outpatient care	213 (55%)
Hospital—outpatient clinic only	87 (23%)
Community clinic	42 (11%)
Primary care or general practice	26 (7%)
Other	18 (5%)
Number of people living with HIV cared for by health-care service	
1–100	16 (4%)
101–1000	136 (35%)
1001–5000	195 (51%)
>5000	35 (9%)
Uncertain or unspecified	4 (1%)
Number of personal consultations with people living with HIV per week	
1–10	69 (18%)
11–50	229 (59%)
51–100	60 (16%)
>100	28 (7%)
Number of people taking long-acting therapy under respondent's care	
1–10	136 (35%)
11–50	165 (43%)
51–100	42 (11%)
>100	43 (11%)

N=total number of respondents.

Table 1: **Phase 1 survey respondent characteristics**

See Online for appendix

	n (%)
In your clinical practice, which definition of virological failure do you use to guide decisions regarding people who are suppressed on LAI CAB+RPV? (N=386)	
HIV viral load more than 200 copies per mL on two consecutive occasions	203 (53%)
HIV viral load more than 50 copies per mL on two consecutive occasions	87 (23%)
HIV viral load more than 200 copies per mL on one occasion	31 (8%)
HIV viral load more than 400 copies per mL on two consecutive occasions	15 (4%)
Any viraemia resulting in a switch of therapy regardless of documented resistance to injectable antiretroviral therapy	12 (3%)
HIV viral load more than 50 copies per mL on one occasion	8 (2%)
HIV viral load more than 400 copies per mL on one occasion	5 (1%)
HIV viral load more than 200 copies per mL plus discontinuation of treatment	4 (1%)
HIV viral load more than 1000 copies per mL on one occasion	4 (1%)
Other	12 (3%)
Not applicable	5 (1%)
Do you think definitions of virological failure should be the same or different for oral and injectable therapy? (N=385)	
Definitions should be the same	266 (69%)
Unsure	67 (17%)
Definitions should be different	52 (1%)
How would you define discontinuation in people on LAI CAB+RPV? (N=114)*	
Patients who have missed one injection + are uncontactable + may or may not have a detectable viral load	55 (48%)
Patients who have missed two injections + are uncontactable + may or may not have a detectable viral load	20 (18%)
Patients who have missed one injection + are contactable + may or may not have a detectable viral load	19 (17%)
Patients who have missed two injections + are contactable + may or may not have a detectable viral load	10 (9%)
Patients who have missed one or more injections + may or may not have a detectable viral load	4 (4%)
Other	6 (5%)
Do you think the definition of treatment discontinuation should be the same or different in people on oral *vs* injectable therapy? (N=114)*	
Definitions should be different	84 (74%)
Definitions should be the same	30 (26%)

LAI CAB+RPV=long-acting injectable cabotegravir and rilpivirine. N=number of non-missing responses for each question. n=number of respondents. *Reduced response due to survey design (see Discussion section).

Table 2: **Definitions of virological failure and treatment discontinuation used for LAI CAB+RPV in clinical practice**

	n (%)
WHO region	
European region	26 (50%)
Region of the Americas	17 (33%)
Western Pacific region	4 (8%)
African region	3 (6%)
South-East Asia region	1 (2%)
Eastern Mediterranean region	1 (2%)
Self-identified sex	
Female	24 (46%)
Male	26 (50%)
Non-binary	2 (4%)
Age	
35–44 years	6 (12%)
45–59 years	25 (48%)
≥60 years	21 (40%)
Years of experience in the field of HIV	
1–10 years	4 (8%)
11–20 years	7 (14%)
21–30 years	17 (33%)
>30 years	24 (46%)
Type of experience	
HIV health-care provider	47 (90%)
Community representative	5 (10%)
Evidence of leadership in field	
HIV national guideline committee member	43 (83%)
HIV international guideline committee member	23 (44%)
Leadership position in national HIV society or research network	42 (81%)
Leadership position in international HIV society or research network	27 (52%)
HIV or infectious disease conference chair	29 (56%)
HIV or infectious disease conference organising committee	36 (69%)
Head of hospital division or department	27 (52%)
Infectious disease journal editorial committee	23 (44%)
Medical journalist	4 (8%)
Representative of organisation for people with lived experience of HIV	5 (10%)

n=number of participants.

Table 3: **Characteristics of the 52 Delphi panellists**

remained consistent when stratified by region and professional background (data not shown).

Consistent feedback in the open-text responses included the need to: specify the time between consecutive viral load testing, with the most common recommendation being 2–4 weeks; specify that the definition is in a context in which people are receiving their injections as expected; add an option for a single viral load of more than 1000 copies per mL to accommodate settings with less sensitive assays or less frequent testing capacity; clarify the relationship between emergent resistance and virological failure; and account for people who initiate LAI cabotegravir and rilpivirine unsuppressed and remain unsuppressed.

The initial definition of LAI cabotegravir and rilpivirine treatment discontinuation (people who have missed one injection and are uncontactable irrespective of viral load) did not reach consensus for any of the validity criteria, including when stratified by region and professional background.

The most common feedback was that the definition of treatment discontinuation addressed loss to follow-up or disengagement from care but not necessarily other reasons for discontinuation of LAI cabotegravir and rilpivirine such as due to pregnancy or side-effects. Other suggestions included: specifying whether oral bridging therapy is considered discontinuation; dropping uncontactable as a criterion; and changing the definition to two missed injections since this is the requirement to

reinitiate treatment with a loading dose in many clinical care contexts. The definitions were revised according to these consistent recommendations.

In round 2 of the Delphi (50 experts, retention of 96%), the revised definitions for virological failure and LAI cabotegravir and rilpivirine treatment discontinuation both reached consensus for all validity criteria (figure 2). No further rounds were conducted in accordance with the closing criteria. Minor recommended revisions in the open-text responses included changing the phrasing from "unable to achieve a viral load", which could be perceived as stigmatising, to "unable to suppress viral load". Remaining open-text responses included concerns about low-level viraemia of 50–199 copies per mL, viral blips (defined as single viral load between 50 and 199 copies per mL with two adjacent viral load <50 copies per mL), and the recommended viral load retesting window.

After addressing the recommended minor revisions, the final consensus definition of virological failure was: (a) viral load of 200 copies per mL or more on two occasions 2–4 weeks apart, or (b) a single viral load of more than 1000 copies per mL, and/or (c) emergent resistance, in the context of timely injections and prior suppression of less than 200 copies per mL; OR (d) unable to suppress viral load to less than 200 copies per mL on continuous therapy.

The final consensus definition of treatment discontinuation was: people on LAI cabotegravir and rilpivirine who have missed two consecutive injections and have not taken oral bridging in the interim, irrespective of reason for discontinuation (figure 2).

Discussion

The phase 1 international survey highlights inconsistencies in definitions of virological failure and treatment discontinuation for LAI cabotegravir and rilpivirine in clinical practice. These inconsistencies could reflect different interpretations of the evidence but might also suggest that clinicians are not as comfortable managing elevated viraemias in people receiving LAI cabotegravir and rilpivirine, likely a result of this regimen being the first LAI therapy. It might also be related to concerns about the low but present risk of resistance should virological failure occur, with some clinicians using much more stringent virological failure definitions (such as isolated unconfirmed viraemia of any numerical value) rather than accepted definitions used in RCTs.[10–11] These uncertainties in clinical practice are reflected in how observational studies of LAI cabotegravir and rilpivirine are being reported, which in turn complicates interpretation of findings and might affect clinical decision making (eg, premature discontinuation based on what might amount to a viral blip).[15–18] This discontinuation on account of a viral blip is not supported by the available evidence from blip analyses of LAI cabotegravir and rilpivirine RCTs,[29] which have not

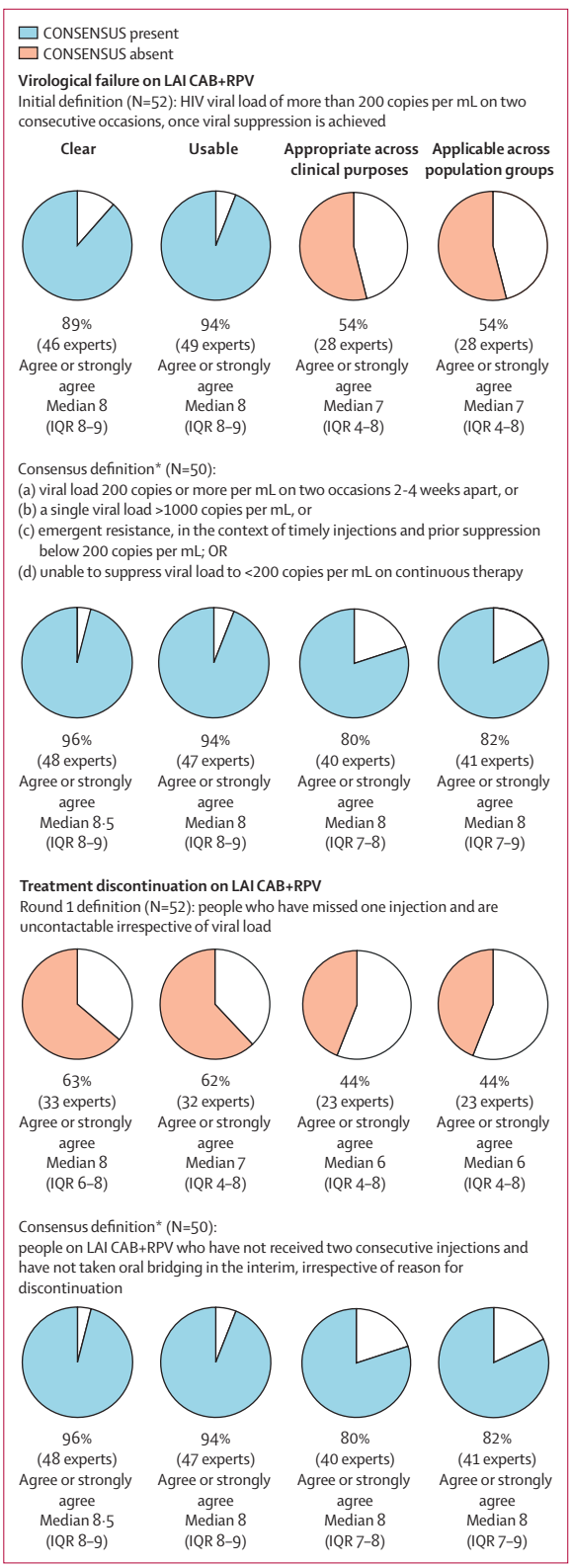

Figure 2: **Delphi results and consensus definitions**
Agree or strongly agree was rated on a Likert scale of 1 (strongly disagree) to 9 (strongly agree). LAI CAB+RPV=long-acting, injectable cabotegravir and rilpivirine. N=total number of participants. *Includes minor revisions according to round 2 open-text feedback.

shown any association between viral blips (defined as single viral load between 50 and 199 copies per mL with two adjacent viral loads <50 copies per mL) and virological failure.

The threshold of 200 copies per mL agreed upon in the consensus definition of virological failure is consistent with definitions used in clinical trials[1–3] and widely adopted clinical guidelines.[10–13] The threshold also aligns with the undetectable=untransmittable (U=U) principle, which is supported by strong evidence showing that maintaining an HIV viral load of less than 200 copies per mL prevents sexual transmission.[11] This principle is reflected in public health messaging that people living with HIV who sustain viral suppression of less than this threshold can live long, healthy lives without transmitting the virus.[11] To avoid ambiguity, the definition of virological failure in this study specifies that HIV RNA of 200 copies per mL or more on any two occasions 2–4 weeks apart qualifies as virological failure, regardless of whether the measurements are consecutive; the date of virological failure in this situation is the date HIV RNA of 200 copies per mL or more is confirmed. This time window is intended to provide guidance on scheduling repeat testing while allowing for some flexibility in follow-up intervals. However, it is hoped that clinicians would use this flexibly to guide decisions when the interval for repeat testing falls slightly outside this window (eg, by 1 week).

The alternative criterion of a single viral load greater than 1000 copies per mL accounts for the low availability of viral load testing in many settings and the variability in viral load detection limits across different tests and sample types.[30] This criterion aligns with the WHO's threshold for virological failure.[30]

The final virological failure criterion, unable to suppress viral load to less than 200 copies per mL on continuous therapy, is a forward-looking, theoretical definition, as LAI cabotegravir and rilpivirine is not licensed for individuals with an unsuppressed viral load. To ensure consistency with viral load evaluation points in clinical trials we recommend considering continuous therapy as receiving on-time injections for at least 12–24 weeks.[3] These durations are standard entry criteria for switch studies in individuals who are virally suppressed. However, further clinical data on LAI cabotegravir and rilpivirine use in unsuppressed individuals are needed to determine the optimal monitoring period before the absence of suppression can be regarded as as virological failure.

The definition of treatment discontinuation specifies that it occurs when a second scheduled injection is missed in the absence of bridging therapy. This definition aligns with the point at which an individual would typically require reinitiation or transition to an alternative regimen in clinical practice. For consistency, this means that the date of treatment discontinuation is defined as the scheduled date of the second missed injection. Treatment discontinuation in our study refers specifically to the discontinuation of cabotegravir and rilpivirine treatment rather than antiretroviral treatment interruption in general. As such, switching to a different regimen would be considered treatment discontinuation of cabotegravir and rilpivirine. The definition can be applied regardless of the reason for discontinuation, including virological failure. Defining treatment discontinuation by number of missed injections rather than period since last injection was preferred due to differences in scheduling intervals (4 weeks *vs* 8 weeks). However, this definition might need to be reviewed if substantially longer duration formulations become available.

Despite differences in primary objectives between researchers (reliable outcomes) and clinicians (optimal patient safety), there was strong agreement among experts within the Delphi panel that establishing shared definitions is both important for ensuring safe clinical care and feasible to implement. In this study, the ability to reach agreement among a diverse, global group of experts working in countries with variable income levels in just two rounds underscores this feasibility. The definitions reached for both virological failure and treatment discontinuation were multifaceted, incorporating nuances related to the clinical cohort (individuals who are virally suppressed *vs* unsuppressed) and recognising the key role of emergent resistance and differing pharmacokinetics when using observed dosing LAI cabotegravir and rilpivirine.

Consensus about the definitions in this study provide a foundation for aligning treatment practices in the reporting of observational cohorts and valuable information for consideration by guideline committees. There was a clear awareness among clinicians that viral blips and low-level viraemia (50–199 copies per mL) still need to be carefully managed, including ensuring injections are administered on time, checking for contraindications or drug interactions, and monitoring viral load frequently. As additional LAI therapies emerge, it is important to have a common definition of treatment discontinuation, which is based on receipt of an injection and differs appropriately from previous definitions of treatment discontinuation created for oral therapy.

Strengths of this study include a very high retention rate of senior experts on the panel participating in the Delphi process. The process included summarised qualitative feedback, which allowed experts to understand the nuanced views of other experts while maintaining anonymity. This approach facilitated formulating virological failure definitions that address the low but present risk of resistance-associated mutations and enable meaningful future meta-analysis and pooled analysis across observational cohorts regardless of viral load at entry.

Limitations include the fact that survey respondents and Delphi experts were predominantly from regions where LAI cabotegravir and rilpivirine is licensed and has been available for some time, which could affect the

applicability of the definitions to other regions. To mitigate this bias, we purposefully included survey respondents and Delphi experts from countries where LAI cabotegravir and rilpivirine was not yet licensed, but who had experience with the regimen in clinical trials. We also included the category of more than 1000 copies per mL viral load within the virological failure definition. In phase 1, a survey error limited the opportunity to respond to discontinuation questions, which might have introduced a response bias for these questions. However, the effect of this bias on the final study outputs is minimised by the fact that the phase 1 definition of treatment discontinuation was substantially revised during the phase 2 Delphi process. Finally, a limitation of the Delphi design is that all experts' scores are considered equally, even though some experts might have more knowledge in the field or more clinical experience with LAI cabotegravir and rilpivirine.

Further validation of the recommended virological failure thresholds and optimal viral load retesting interval are needed to address ongoing concerns about cabotegravir and rilpivirine resistance. This validation could be achieved through evidence synthesis of existing and emerging data from cohort and RCTs reporting resistance, epidemiological transmission studies, and additional expert review. As the LAI field evolves, periodic review of the consensus definitions would be beneficial to ensure that the definitions remain aligned with best practice, for example through a repeated Delphi every 3–5 years. Future validation of these definitions in settings where viral load testing is less available would be useful if licensing of cabotegravir and rilpivirine proceeds in LMICs. Furthermore, if regulatory approvals expand to new populations, such as to pregnant and lactating individuals, consensus definitions might require reassessment to align with maternal health priorities and prevention of vertical HIV transmission. Definitions might also need to be revised if longer-acting cabotegravir and rilpivirine formulations become available, extending dosing intervals. Additional dissemination of this study will be needed to ensure that clinicians, researchers, and guideline developers are aware of this consensus and utilise the proposed definitions in their clinical practice and observational cohorts.

Contributors

CO, AP, AE, MS, SP, and KR conceptualised the study. CO, KR, and MS acquired the study funding. The methodology was determined by CO, AP, and MS. MS, AP, KR, AE, and CO were involved in survey development and recruitment. CO, AP, and MS had access to all the datasets and verified the underlying data. AP conducted the analysis of the Delphi survey and MS conducted the analysis of the initial health-care provider survey. CO, KR, AV-A, AC, AG, AH, AR, BKT, BS, CF, CPC, CBM, CdR, DRK, DHST, EM, FWNMW, FC, WDFV, IL, JZ, JM-M, JH, JA, JML, JC, JR, JS, KG, LW, MGa, MR, MB, MT, MP, MJ, MGi, NK, NP, NM, PC, RE, SN, SW, SC, SCH, AV-A, WRS, and YG contributed as expert Delphi panellists. AP and CO wrote the first draft of the manuscript with review from all authors. Reviews and edits of subsequent drafts were conducted by all co-authors. All authors approved the final manuscript.

Declaration of interests

CO has received honoraria for advisory boards, lectureships, and travel sponsorships from Janssen, Gilead Sciences, ViiV Healthcare, MSD, and Bavarian Nordic; and has received research grants from Janssen, Gilead Sciences, ViiV Healthcare, MSD, and AstraZeneca. KR has received speaker and consultations fees from ViiV Healthcare; conference sponsorship from Janssen and Gilead; and is an investigator on drug trials sponsored by Gilead Sciences and MSD. AV-A receives consultation fees from AbbVie. AC has received grants from MS, ViiV Healthcare, and Gilead Sciences for unrelated research. AMG has received personal fees from Abbott, Gilead, GSK, MSD, Roche, and ViiV Healthcare; and research funding (paid to institution) form Gilead, Roche, and ViiV Healthcare. AH has received honoraria for consulting from Gilead Sciences and ViiV Healthcare; and grants for research studies from Gilead Sciences. CF has received honoraria for consulting from Gilead Sciences and ViiV Healthcare; and grants to the institution from Gilead Sciences and ViiV Healthcare. CPC has received honoraria for consulting from MSD, GSK, and ViiV Healthcare. CBM has participated in advisory boards, received study grants, and/or speaker honoraria from Abbvie, Gilead, ViiV Healthcare, Janssen, Angelini, BMS, and MSD. DRK receives grant support and/or consulting honoraria from AbbVie, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche, and ViiV Healthcare. DHST is supported by a Canada Research Chair in HIV Prevention and STIs. EM has received research grants from MSD and ViiV Healthcare; consultancy compensation from Janssen, MSD, and ViiV Healthcare; and payments for educational activities from Gilead Sciences, Janssen, MSD and ViiV Healthcare. FWNMW has received consultancy fees from ViiV Healthcare (paid to his institution); and fees for advisory boards from Gilead Sciences and ViiV Healthcare. FC has received grant funding to the institution from ViiV Healthcare, Johnson & Johnson, and Wellcome Trust. WDFV receives funding from the Bill & Melinda Gates Foundation, SA Medical Research Council, National Institutes for Health, Unitaid, Foundation for Innovative New Diagnostics, Merck, and the Children's Investment Fund Foundation; has previously received funding from US Agency for International Development; and receives drug donations from ViiV Healthcare, Merck, J&J, and Gilead Sciences for investigator-led clinical studies. The unit does investigator-led studies with Merck, J&J, and ViiV Heathcare providing financial support; and is doing commercial drug studies for Merck and Novo. The unit performs evaluations of diagnostic devices for multiple biotech companies. WDFV receives honoraria for educational talks and advisory board membership for Gilead, ViiV, Mylan/Viatris, Merck, Adcock-Ingram, Aspen, Abbott, Roche, Johnson & Johnson, Sanofi, Boehringer Ingelheim, Thermo-Fischer, and Virology Education. IL has been a consultant or advisor for Gilead Sciences, GSK, and MSD; provided expert testimony for GSK; received grants from Gilead Sciences; and payment for lectures from Gilead, GSK, MSD, and Pfizer. J-MM has received honoraria for advisory board participation from Gilead Sciences, Merck, and ViiV Healthcare; and received grant funding from Gilead Sciences. JH's institution has received reimbursement for her time on advisory boards for Gilead Sciences and ViiV Healthcare. JML received honoraria for lectures, presentations, or speaker's bureaus from Janssen-Cilag, Gilead Sciences, Thera Technologies, MSD, and ViiV Healthcare, outside of the present work; and received support from Gilead Sciences, Janssen Cilag, and ViiV Healthcare for attending meetings; received consulting fees from ViiV Healthcare, Gilead Sciences, MSD, and Janssen-Cilag; and declares payment for expert testimony from Gilead Sciences. JC has served as a Scientific Advisor for Merck and Company. JR has received honoraria for consulting or speaking at educational events from Abbvie, Boehringer, Gilead Sciences, Janssen, MSD, and ViiV Healthcare; received payment for participation on a data safety monitoring board or advisory board for Abivax; and is a European AIDS Clinical Society Board Member. JS has received honoraria, lecture fees, and conference support from Gilead, Merck, GSK, and ViiV Healthcare; and declares research grants from Gilead and Merck. KG has received royalties from UpToDate; was an uncompensated advisor to Pfizer; and has consulted for Shionogi, Spark HealthCare, Premier HealthCare, Harrison Consulting, and MedEd Learning. LW has received speaker or advisory fees from ViiV Healthcare, MSD, and Janssen; and she is an investigator in trials sponsored by Gilead. MG received research grants from Gilead Sciences and honoraria as speaker; and was a Data Safety Monitoring Board committee member

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Data sharing

De-identified participant data collected, including individual participant data, will be made available from the corresponding author on reasonable request.

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