USE OF GENOTYPIC HIV DNA TESTING: A DELPHI-TYPE CONSENSUS Short running title: Delphi Consensus on Genotypic HIV DNA Testing

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Short running title: Delphi Consensus on Genotypic HIV DNA Testing

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Abstract

Objectives:

As many disparities in the clinical use of HIV DNA sequencing are observed, a DELPHI-type consensus was initiated in France to homogenize use, techniques, and interpretation of results.

Methods:

Based on a literature review and clinical experience, a Steering Committee (SC) of eight virologists and one infectious disease specialist formulated statements. Statements were submitted to an independent and anonymous electronic vote of virologists and HIV clinicians in France, between October and December 2022.

Results:

The SC developed 20 statements grouped into six categories: *clinical situations for the use of HIV DNA genotyping; techniques for performing HIV DNA genotyping; consideration of APOBEC mutations; genotyping results reporting; recycling of antiretrovirals; availability of HIV DNA genotyping tests and delays.* Twenty-one virologists and 47 clinicians participated in two voting rounds and 18/20 (90%) assertions reached a 'strong' consensus. For example, that prior genotyping on HIV DNA is useful for clinical decision-making when considering switching to some long-acting regimens or to reduce the number of antiretroviral agents in virologically suppressed patients for whom RNA data are unavailable / not exploitable / not sufficiently informative. Two statements achieved no consensus: reporting any detected viral minority population for discussion in multidisciplinary meetings (virologists), and possible risk of virologic failure when using a second generation InSTI + XTC regimen in patients with undetectable viral load ≥1 year and in the presence of a documented *M184V* mutation <5 years (clinicians).

Conclusion:

This DELPHI-type consensus will facilitate the strengthening and harmonization of good practice when performing HIV DNA sequencing.

1. Introduction

Human Immunodeficiency Virus-1 infection has become a manageable chronic disease with the availability of antiretroviral therapies.[1, 2] Lifelong treatment is currently required to obtain and maintain viral suppression. Either prior to initiation of ART or in the event of suboptimal response to ART, HIV drug resistance testing using plasma HIV RNA plays a key role in guiding treatment choices and optimization.[1,2] When switching to a new ART regimen due to toxicities, for simplification, drug reduction, or a long-acting regimen, it is also recommended to first check HIV genotyping data.[2] In these situations, HIV viral load (VL) usually under 50 copies/mL does not allow amplification for RNA drug resistance testing.[3]

In recent years, there has been growing interest in how HIV drug resistance testing using cellular HIV DNA could assist in clinical decision-making in the event of switching ART, especially when plasma HIV RNA genotype testing is not possible.[4-6] The 2022 European AIDS Clinical Society (EACS) guidelines state that "Proviral DNA genotyping may be useful in persons with multiple virologic failures, unavailable resistance history or low-level viremia at the time of switch".[2] European and French guidelines indicate that it is possible to perform genotypic resistance tests on HIV DNA from Peripheral Blood Mononuclear Cells (PBMCs) in the absence of historical data on plasma viral RNA.[2,7] This test should be interpreted with caution since it has a good positive predictive value but a low negative predictive value.[7]

However, while these guidelines provide general guidance on the indications for cell-associated total HIV DNA resistance testing, practical recommendations to virologists and HIV clinicians are lacking, particularly regarding frequent specific ART switch situations, technique, and interpretation of results.

Since many disparities in clinical practice have been observed, both in the literature and in clinical practice, a modified DELPHI consensus research project was conducted in France

with the aim of homogenizing situations in which HIV DNA sequencing could be used and guiding interpretation of results.

2. Material and methods

The Delphi method is an iterative consensus approach based on information collected from a panel of voters with expertise in the subject under consideration.[8-16] This approach has been widely used in many therapeutic areas and several times in HIV care.[17-28] Using this structured approach, voting experts give their opinion individually and anonymously, and express their degree of agreement on statements in order to achieve consensus on a specific and well-defined subject.

In accordance with both French and international methodologies,[9-12,29] our study was structured as a modified national Delphi consensus and conducted among French hospital clinicians and virologists between September and December 2022. The opinion of voting experts was collected during two assessment rounds using a questionnaire developed by a Steering Committee (SC) (Figure 1).

As recommended by the French National Authority for Health (HAS), voters specified their level of agreement with the statements using a 9-point Likert scale ranging from 1 “Strongly disagree” to 9 “Strongly agree”.[29-31] The percentage of scores and the median were calculated for each statement separately in each voting round. Consensus for a statement was considered ‘strong’ when >75% of the scores were ≥7 and the median score was ≥8, ‘good’ when only one of these two parameters was satisfied, and ‘lacking’ when none of the parameters was satisfied.[9,10,32]

Steering Committee (SC)

The SC included one infectious disease specialist and eight virologists directed by the last author of this article. Two initial SC meetings were held in June and August 2022.

Voting Group

Two voter profiles were identified: virologists and HIV clinicians. A list of voters was compiled based on the following criteria: experience, acquired knowledge and expertise in HIV care, presenting in national conferences or involvement in HIV care projects, with recruitment throughout France, including French overseas territories. The voters were invited via individual e-mails to participate in online voting, with personalized access via a dedicated website. Questions on techniques for performing HIV DNA genotyping were voted on by virologists only. The anonymity of both voting groups was guaranteed. Voters had no interaction with the SC, and SC members did not vote.[29]

Voting Round #1

During this first round of voting, a free text space for comments was made available enabling voters to develop or explain their opinion for each statement. At the end of the first round, scores and voter comments were summarized for each statement.

A third SC meeting took place in November 2022 to discuss the Round #1 results:

- Statements that achieved a 'strong' consensus (i.e., ≥75% of scores ≥7 AND median ≥8) were validated in full and included in the final summary.
- Statements that achieved a 'good' consensus (i.e., ≥75% of scores ≥7 OR median ≥8) were discussed and proposed for Voting Round #2 only when the SC was able to develop a revised version based on analysis of voter comments.
- Statements that did not achieve consensus were re-worded by the SC based on feedback from voters and submitted for Voting Round #2.

Voting Round #2

Only voters from Voting Round #1 were invited to participate in Voting Round #2 to assess the statements amended by the SC from Voting Round #1 results. The free text comment option was deleted but replaced with an 'I don't know' option instead of the scoring response.

Votes including this 'I don't know' option were excluded from the analysis. Following the results of Voting Round #2, the SC closed the process.

Ethical considerations

This research was conducted in accordance with the Declaration of Helsinki. All personal data transmitted for the study was separated from the results and anonymized, pursuant to the French data protection law (GDPR – General Data Protection Regulation).

3. Results

Based on a literature analysis, existing guidelines and clinical experience, the SC initially developed 21 statements (two were subsequently merged resulting in 20 statements) divided into 6 key areas: *clinical situations for the use of HIV DNA genotyping; techniques for performing HIV DNA genotyping; consideration of APOBEC mutations; genotyping results reporting; recycling of antiretrovirals; availability of HIV DNA genotyping tests and delays.*

Participation

Voters in Round #1 included 21 virologists and 47 clinicians. All virologists (21/21, 100%) and 40 clinicians out of 47 (85.1%) from Round #1 actively voted in Round#2.

A summary of the characteristics of voters is shown in Table 1. The virologists were 76% (n=16) full-time hospital workers, 10% (n=2) part-time and 14% (n=3) engineers ('Others'). Their median experience in performing HIV DNA sequencing was 10 years (IQR [5-12]) and the median number of HIV DNA genotypes performed per year was 225 (IQR [42.5-425]). Clinicians were 94% (n=44) full time hospital workers and 6% (n=3) part time. Their median experience with people living with HIV (PLWH) management was 25 years (IQR [15-31.5]) and the median number of patients they followed per year was 270 (IQR [200-400]).

All virologists and clinicians had extensive experience in HIV care-related activities over the previous five years, such as writing conference abstracts (76% and 83% respectively), writing scientific publications (76% and 74%), participating in research projects (100% and 91%),

involved in training (81% and 81%), belonging to a professional or associated group (76% and 81%) and speaking at scientific events (52% and 68%).

Statements (Table 2)

After Voting Round #1, 9/21 statements achieved a 'strong' consensus (≥75% votes ≥7 and median ≥8); 5/21 statements achieved a 'good' consensus (≥75% votes ≥7 or median ≥8) and 7 statements lacked a consensus: 12 statements were revised by the SC for Voting Round #2, including all those which achieved a 'good' consensus and all those which did not achieve a consensus, of which two were merged resulting in 20 statements. After Voting Round #2, 9/11 revised statements achieved a 'strong' consensus, and two statements did not achieve a consensus. In total, 18/20 statements (90%) achieved consensus. The distribution of cumulative votes, medians and results are provided in Table 2.

Consensus statement results (See Table S1 for Consensus results according to voter group, and Table S2 for Statements, detailed virologists and clinicians voting results, and cumulative results for both groups).

<u>Clinical situations for the use of HIV DNA genotyping</u>

In the context of a therapeutic decision requiring genotyping data, there was a 'strong' consensus from voters on the recommendation to perform HIV DNA genotyping when HIV RNA is non-amplifiable, when cumulative HIV RNA genotyping is not available and/or when the historical genotype is incomplete or unusable. Voters recognized with a 'strong' consensus that for the following therapeutic targets - reverse transcriptase, protease, integrase - HIV DNA sequencing has a good positive predictive value towards mutation detection (excluding APOBEC mutations) and an imperfect negative predictive value.

Voters also 'strongly' agreed that, in a virologically suppressed patient, in the absence of exploitable or sufficiently informative RNA data, and when considering a drug-reduction / simplification of the antiretroviral (ARV) regimen:

- for a switch to some long-acting regimens, prior HIV DNA genotyping is useful for clinical decision-making,

- for sequential dosing (4 days out of 7 or 5 days out of 7) without changing any ARV in the current regimen, it is not mandatory to prior perform HIV DNA genotyping for clinical decision-making,

- for a reduced ARV number regimen, prior HIV DNA genotyping may be useful for clinical decision-making.

Techniques for performing HIV-DNA genotyping

Virologists validated with a 'strong' consensus that, in current practice, HIV DNA genotyping has a decreased performance (sensitivity, representativeness of viral populations) when the DNA quantity is very low. It can be performed indifferently from whole blood, mononuclear cells isolated from peripheral blood or blood cell pellets, and although performance could be increased by performing duplicate, duplicate is not feasible in clinical practice.

Concerning HIV DNA genotyping techniques, virologists agreed with a 'strong' consensus that Sanger or ultra-deep sequencing (UDS) could be used. However, there was an absence of consensus on the relevance of discussing any viral minority population (i.e. variants below 15 to 20% of the viral population) detected after using UDS techniques in a multidisciplinary meeting in the absence of defined clinically relevant detection threshold, according to the current state of knowledge ('no consensus'; with the exclusion of 1/21 (4.7%) virologists who answered 'I don't know').

Consideration of APOBEC mutations

The cytidine deaminases APOBEC3F and 3G enzymes might introduce G to A nucleotide mutations that can impair crucial enzymatic sites or generate stop codons that reduce the amount of replication competent proviruses.[33-36] Voters validated with a 'strong' consensus

that the detection of the *M184I* mutation in HIV DNA is suggestive of the presence of a defective genome in the APOBEC enzyme when associated with other evocative mutations (e.g., *M41I, M230I* on reverse transcriptase) and/or stop codons. They also recognized with a 'strong' consensus that, when resistance mutations attributable to APOBEC are present, their significance should be interpreted with caution according to the clinical context and therapeutic history of the patient and should be indicated in the HIV DNA genotyping analysis report.

Reporting of genotyping results

With a 'strong' consensus, virologists and clinicians felt that the clinical interpretation of resistance mutations on HIV DNA genotyping should be discussed in multidisciplinary meetings. They also agreed that the detection via HIV DNA sequencing of new resistance mutations (excluding APOBEC and stop codons), which were previously undetected, must be considered for the switch decision and subsequent patient follow-up.

ARV recycling

Virologists and clinicians agreed with a 'strong' consensus that, in a patient with an undetectable viral load for at least one year and with documented *M184V* substitution on the current DNA genotype and/or on an RNA genotype performed within the last five years, the use of a 2nd generation InSTI (Integrase Strand Transfer Inhibitor) + XTC (Lamivudine or Emtricitabine) + 1 NRTI combination is at low risk of virological failure over time. Virologists validated with a 'strong' consensus that, under the same conditions, the use of a 2nd generation InSTI + XTC combination may present a risk of virological failure over time. However, clinicians remained divided on this possible virological risk and their vote did not reach a consensus ('no consensus', no clinicians answered 'I don't know').

With a 'strong' consensus, virologists and clinicians validated that the use/recycling of NNRTIs, if resistance to this class was detected in HIV-DNA and/or in previous historical genotypes, is associated with a greater risk of virological failure, independently of the

duration of undetectable viral load, particularly in drug-reduction strategies using this ARV class.

Availability of HIV DNA genotyping tests and time to report results

With a ‘strong’ consensus, virologists and clinicians felt that genotypic HIV DNA testing should be accessible in clinical practice to all clinicians managing PLWH, and that results from these tests should be available within 30 days.

4. Discussion

This consensus research, using the DELPHI method, aims at harmonizing HIV DNA sequencing practices.

All five assertions on clinical situations for use of HIV DNA genotyping developed by the SC were validated with a ‘strong’ consensus by the voters. Although HIV DNA sequencing is not routinely recommended[2] and does not systematically reveal the same results as those previously detected by cumulative plasma RNA genotyping in virologically controlled patients,[4,5] it is useful to perform in several clinical circumstances. This is the case when historical HIV RNA resistance data are insufficient and/or incomplete, or when the viral load is too low to proceed with HIV RNA sequencing. A recent study - based on a very large genotypic database in France - describing the prevalence of genotypic baseline risk factors for some long-acting regimen failures among ARV-naive patients showed that 10.1% of patients displayed one baseline virological risk factor for virologic failure.[37] These findings emphasize the need to check the genotypic resistance profile prior to initiating a long-acting regimen to limit the potential risk of virologic failure and the emergence of resistance.

However, in the case of a virologically suppressed patient, in the event of a decision to reduce or simplify sequential treatment (4 days or 5 days out of 7) without changing the regimen, there was a ‘strong’ consensus that prior genotyping of HIV DNA is not essential to clinical decision-making, even in the absence of usable or sufficiently informative RNA data. This

matches literature findings showing that triple combination therapy of a 2nd generation InSTI + XTC + 1 NRTI administered every 4 or 5 days maintains control of HIV replication in virologically suppressed PLWH while reducing cumulative exposure to ARV.[38,39]

There was a 'strong' consensus from virologist voters that HIV DNA sequencing should be performed when the viral quantity is sufficiently high (since the quantity of HIV DNA influences the quality of the results obtained), that it can be used from different blood sample matrix, indifferently by Sanger or UDS, and that duplicates increase test performance (although this cannot be used in current clinical practice). Nevertheless, knowing HIV-DNA genotyping underestimate resistance detection due to a phenomenon of dilution of resistant species in the reservoir regardless of the sequencing method used, UDS methods might improve resistance detection in HIV-DNA due to their greater sensitivity.[40-42] Virologists were unable to reach a consensus on the fact that, given the current state of knowledge, it may be worthwhile reporting any minority viral population detected for discussion in a multidisciplinary discussion. They also didn't support the idea that it might be useful to report any minority viral population detected for multidisciplinary discussion in the current context of an undefined detection threshold for UDS techniques.

Although the 1% threshold for UDS techniques was found to be close to the sensitivity obtained in historical HIV RNA resistance tests,[41] it was difficult for the SC to generate a statement for voting with such a detection threshold. This is due to the variability of this threshold depending on the UDS technique used, and the lack of solid evidence on the impact of a minority variant as low as 1% on virological failure for newer ARVs with a high barrier to resistance. Considering that UDS on HIV-DNA is now affordable in clinical practice and may become the future the potential new gold standard in the future, the definition of a technical cut-off to warrant enough sequencing accuracy and a clinical cut-off to establish the clinical relevance of minority variants on treatment switch in virologically suppressed patients are still unmet needs. So further research into these thresholds for both RNA- and DNA-based techniques is warranted.

As shown in the literature,[43,44] the detection of the *M184I* mutation in HIV DNA suggests the presence of a defective genome due to the APOBEC enzyme when associated with other suggestive mutations (See Table S3 for the list of mutations)[36] and/or stop codons, and a 'strong' consensus was reached on this statement. The presence of *M184I* mutation can impair the activity of XTC and possibly some nucleoside reverse transcriptase translocation inhibitors (NRTTIs). These mutations should be considered possible artifacts if they occur at the same threshold at which multiple signature APOBEC mutations are also present.[45] When resistance mutations attributable to APOBEC are detected, it is recommended that their significance should be interpreted with caution[37] and should be indicated in the HIV DNA genotyping analysis.

The French National Authority for Health already recommends that the interpretation of results from a DNA-based genotypic resistance test requires consultation between clinician and virologist.[46] In this context, a 'strong' consensus was reached on the need to discuss clinical interpretation of resistance mutations obtained by HIV DNA genotyping at multidisciplinary discussions. This was also the case regarding clinical decisions about switching ART and patient follow-up in newly detected resistance mutations.

The question of how resistance mutations are 'archived' over time remains important for the potential re-use of specific ARVs. A recent study investigated the kinetics of the *M184V* mutation in proviral HIV DNA in long-term virologically suppressed patients.[47] The authors showed significant progressive clearance of the *M184V* mutation in proviral HIV DNA over the five years of the study. In the presence of a detected M184V substitution over the past 5 years, the SC looked for consensus statements on ARV recycling practices. In this context, the SC proposed statements on ARV recycling practices in the event of the presence of an M184V substitution detected within the last five years.

Regardless of the finding of an *M184V* mutation in the DNA genotype and clearance kinetics of the mutation, it has been observed that, in patients virologically suppressed for at least one year, the use of a 2nd generation InSTI + XTC + 1 NRTI regimen presents a low risk of

309 virological failure over time.[48] The voters ‘strongly’ endorsed this statement. However, when
310 a M184V mutation has been documented over the past five years in a virologically suppressed
311 patient, the virologist voters ‘strongly’ agreed that the use of a 2nd generation InSTI + XTC
312 regimen could present a risk of virological failure over time, as described in some literature.[49]
313 For documented NNRTI mutations, there was a ‘strong’ consensus that the recycling of this
314 ARV class is associated with an increased risk of virological failure, irrespective of the
315 duration of viral suppression, particularly in drug reduction strategies and long-acting
316 regimens using this ARV class.[50]
317 Since HIV DNA sequencing adds an important contribution to many clinical situations and
318 patient follow-up,[2] there was a ‘strong’ consensus that it should be accessible to all
319 practitioners. Also, that its results should be received within one month. The literature rarely
320 provides such an indication of time in which to report results but, with current HIV DNA
321 sequencing methods being faster than before, this timeframe seems reasonable.[51]
322 The Delphi method is known as a structured procedure which enables many experts to be
323 consulted individually and anonymously on a specific subject while guaranteeing free
324 expression of each voter. However, this approach has some limitations associated with voters’
325 profiles, statements elaboration and criteria considered to achieve a consensus.[52] Our research
326 sought to limit these potential biases as far as possible to ensure maximum objectivity.
327 Although voters were recruited only in France, they were selected on objective criteria based
328 on their experience and expertise in HIV care and HIV virology. These criteria yielded a voter
329 sample with reassuring characteristics: a median of 10 years' experience performing HIV
330 DNA sequencing in the virologists' group and a median of 25 years' experience in PLWH
331 management in the clinicians’ group. As far as the SC statements are concerned, a literature
332 review made it possible to identify key questions raised in clinical practice and propose
333 precisely worded statements. In terms of the threshold used to reach consensus, our study was
334 based on a rigorous two-criteria approach. This strict and demanding definition lends a high
335 degree of credibility to our results. To ensure the virologist panel represented the whole of

France territory, the SC supported identification of some virologists. Finally, our research was conducted with a continuous and complete separation between voters who voted anonymously and SC members who neither participated in the vote nor interacted directly with voters. The constraint inherent in this separation was the absence of direct exchanges between voters and SC members: such exchanges could have been useful when revising statements for voting Round #2. Furthermore, like all Delphi-type consensus, the findings represent good practices for virologists and clinicians who remain masters of their own practice and must adapt findings to individual patient circumstances.

In conclusion, in this consensus research using the Delphi method, 18/20 (90%) statements achieved a consensus. Only two assertions did not reach consensus. Virologist voters remained divided on the value of discussing any minority population detected at a multidisciplinary meeting, and the clinician voters remained divided on the possible virological risk of using a combination of a 2nd generation InSTI + XTC in HIV suppressed patients of more than one year in the presence of a documented M184V mutation of less than five years.

Our consensus findings constitute a solid basis for implementation and homogenization of practice regarding the use of DNA HIV sequencing, its performance, and its reporting, particularly when needing to reduce the number of ARV agents and when using some long-acting regimens.

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Figure 1: Modified Delphi process chart

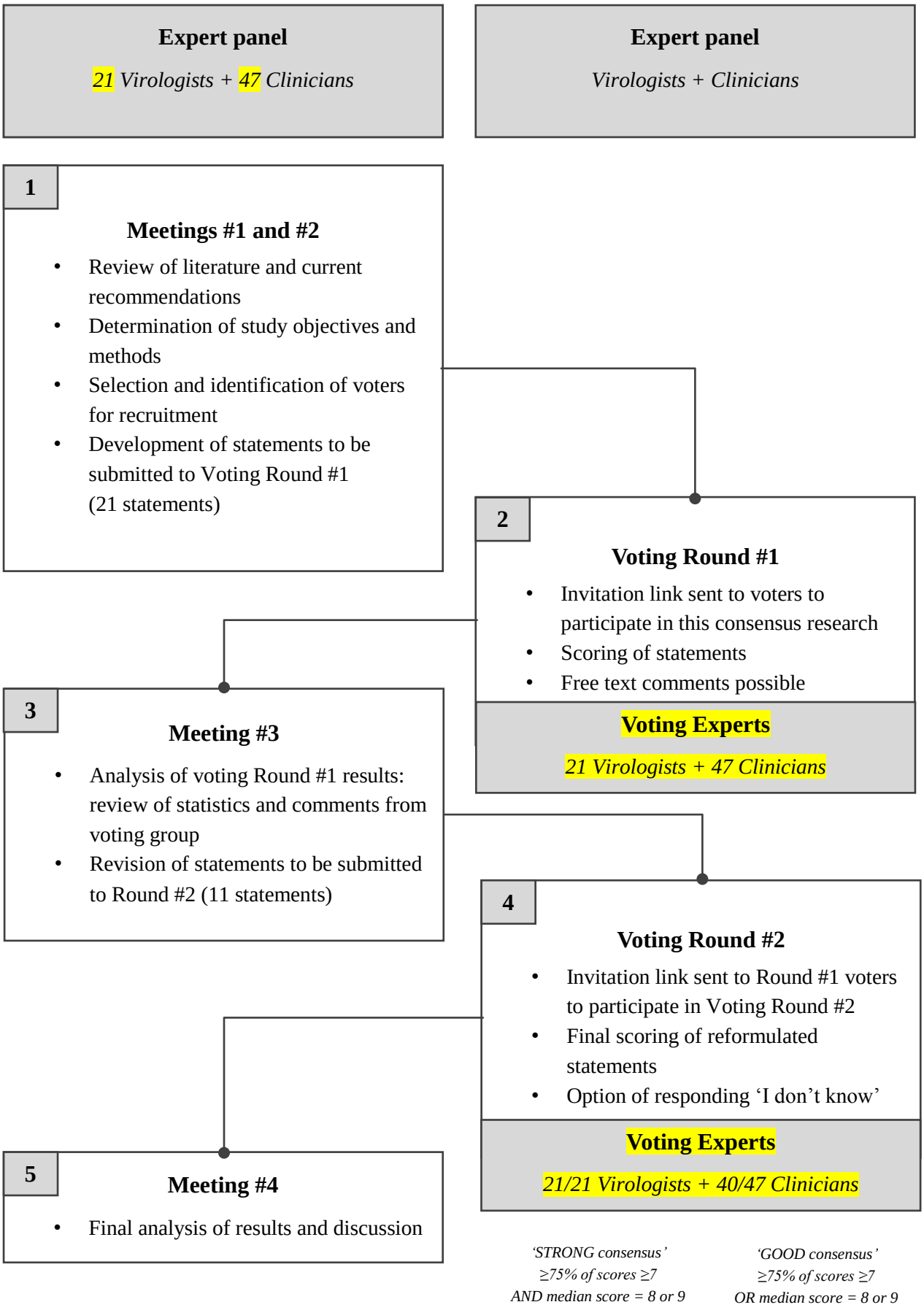

Table 1 – Characteristics of voters

Characteristic	**Virologists** (n = 21)	**Clinicians** (n = 47)
Age, median [IQR], years	46 [43-55]	56 [46-60.5]
Gender F/M, n (%)		
Female	16 (76)	18 (38)
Male	5 (24)	29 (62)
Type of practice, n (%)		
Full-time hospital workers	16 (76)	44 (94)
Part-time hospital workers	2 (10)	3 (6)
Others	3 (14)	-
Years of experience performing HIV DNA sequencing, median [IQR], years	10 [5-12]	-
Number of HIV DNA genotypes performed per year, median [IQR]	225 [42.5-425]	-
Years of experience in PLWH management, median [IQR], years	-	25 [15-31.5]
Number of PLWH seen per year, median [IQR]	-	270 [200-400]
Experience in HIV care-related activities in the past 5 years, n (%)		
Conference abstract	16 (76)	39 (83)
Scientific article	16 (76)	35 (74)
Research project (not including this study)	21 (100)	43 (91)
Involved in training	17 (81)	38 (81)
Professional or associate group or member	16 (76)	38 (81)
Speaker at scientific events	11 (52)	32 (68)

DNA: desoxyribonucleic acid; F: Female; M: Male; PLWH: People living with HIV

Table 2 - Statements and cumulative voting results for virologists and clinicians

For each statement, a total number of voters equaling 21 indicates that only virologists were invited to vote and a total number of voters different from 68, 61, or 21 indicates the use of the ‘I don't know’ option by voters during the second voting round.

	STATEMENTS	Scores 1-2-3 (n)	Scores 4-5-6 (n)	Scores 7-8-9 (n)	Median	Results
Clinical situations for the use of HIV DNA genotyping						
1	In the context of a therapeutic decision requiring genotyping data, when HIV RNA is not amplifiable, when cumulative HIV RNA genotyping is not available and/or or in the event of an incomplete or unusable genotypic history, HIV DNA genotyping is recommended.	2.9% (2)	7.4% (5)	89.7% (61)	9	**Strong consensus**
2	For the following therapeutic targets - reverse transcriptase, protease, integrase - HIV DNA sequencing has a good positive predictive value (excluding APOBEC mutations) and an imperfect negative predictive value.	2.9% (2)	13.2% (9)	83.8% (57)	8	**Strong consensus**
3	In the context of a patient who has achieved virological success, in the event of a decision to reduce or simplify treatment to some long-acting regimens, prior genotyping on HIV DNA is useful for clinical decision-making in the absence of usable or sufficiently informative RNA data.	5.9% (4)	13.2% (9)	80.9% (55)	8	**Strong consensus**
4	In the context of a patient with virological success, in the event of a decision to reduce or simplify sequential treatment (4 days out of 7 or 5 days out of 7) without changing the treatment molecules, prior genotyping on HIV DNA is not essential for the clinical decision, even in the absence of usable or sufficiently informative RNA data.	13.3% (8)	10% (6)	76.7% (46)	8	**Strong consensus**
5	In the absence of usable or sufficiently informative RNA data, in the case of a patient with virological success, in the event of a decision to reduce/simplify to a treatment that reduces the number of ARV, prior genotyping on HIV DNA may be useful for clinical decision-making.	8.2% (5)	13.1% (8)	78.7% (48)	8	**Strong consensus**
Techniques for performing HIV DNA genotyping						
6	In current practice, when the amount of DNA is very low, the performance (sensitivity, representativeness of viral populations) of HIV DNA genotyping is reduced.	5.3% (1)	5.3% (1)	89.5% (17)	9	**Strong consensus**
7	In current practice, genotyping on HIV DNA can be performed either from whole blood, from the cells isolated from peripheral blood (PBMC) or from blood cell pellets.	14.3% (3)	9.5% (2)	76.2% (16)	8	**Strong consensus**
8	Duplicate DNA genotyping increases performance (sensitivity, representativeness of viral populations) but is not possible in current practice.	10.5% (2)	5.3% (1)	84.2% (16)	8	**Strong consensus**
9	Sanger and ultra-deep sequencing can be used to perform HIV DNA genotyping.	0% (0)	23.8% (5)	76.2% (16)	8	**Strong consensus**
10	For ultra-high throughput DNA sequencing techniques (ultra-deep sequencing), with the current state of knowledge, the clinically relevant detection threshold is not defined. Nevertheless, it may be interesting to report any viral minority population detected for multidisciplinary discussions.	10% (2)	25% (5)	65% (13)	7.5	**NO CONSENSUS**
Consideration of APOBEC mutations						
11	Detection of the *M184I* mutation in HIV DNA is suggestive of the presence of a defective genome due to the APOBEC enzyme when it is associated with other suggestive mutations (e.g., *M41I*, *M230I* on reverse transcriptase) and/or stop codons.	1.9% (1)	13.2% (7)	84.9% (45)	8	**Strong consensus**
12	When resistance mutations attributable to APOBEC are present, their significance should be interpreted with caution and based on the clinical context and treatment history.	5.2% (3)	5.2% (3)	89.7% (52)	9	**Strong consensus**
13	The presence of resistance mutations attributable to APOBEC should be reported in the HIV DNA genotyping analysis.	9.5% (2)	4.8% (1)	85.7% (18)	8	**Strong consensus**
Reporting of genotyping results						
14	The clinical interpretation of resistance mutations on HIV DNA genotyping should be discussed at multidisciplinary consultation meetings.	4.4% (3)	17.2% (10)	80.9% (55)	8	**Strong consensus**
15	In a patient with virological success, the detection on HIV DNA genotyping of new resistance mutations (excluding APOBEC & stop codons) previously undetected must be considered for the	5% (3)	10% (6)	85% (51)	8	**Strong consensus**

	switch decision and subsequent follow-up.					
ARV recycling						
16	In a patient with an undetectable viral load for at least one year, in the presence of a documented M184V substitution over the past five years, the use of a 2nd generation InSTI + XTC + 1 NRTI combination presents **low risk** of virological failure over time.	7.4% (5)	7.4% (5)	85.3% (58)	8	**Strong consensus**
17	In a patient with an undetectable viral load for at least one year, in the presence of a documented M184V substitution over the past five years, the use of a 2nd generation InSTI + XTC combination **might present** a risk of virological failure over time.	21.3% (13)	14.8% (9)	63.9% (39)	7	**NO CONSENSUS**
18	The use / recycling of NNRTIs in the event of documented resistance to ARV of this class is associated with a greater risk of virological failure, independently of the duration of undetectable viral load, especially in drug-reduction strategies using this ARV class.	1.7% (1)	18.3% (11)	80% (48)	8	**Strong consensus**
Test availability and delays						
19	HIV DNA genotypic tests should be accessible in clinical practice to all clinicians managing PLWH.	8.8% (6)	7.4% (5)	83.8% (57)	9	**Strong consensus**
20	Reports of genotypic HIV DNA test results should be sent to clinicians within 30 days.	6.6% (4)	9.8% (6)	83.6% (51)	9	**Strong consensus**

ARV: Antiretrovirals; APOBEC: Apolipoproteins B mRNA editing enzyme; InSTI: Integrase Strand Transfer Inhibitor; XTC: Lamivudine or Emtricitabine; PLWH: People living with HIV.

Table S1 – Consensus results according to voter groups

	STATEMENTS	Results VIROLOGISTS	Results CLINICIANS	CUMULATIVE Results
Clinical situations for the use of HIV DNA genotyping				
1	In the context of a therapeutic decision requiring genotyping data, when HIV RNA is not amplifiable, when cumulative HIV RNA genotyping is not available and/or or in the event of an incomplete or unusable genotypic history, HIV DNA genotyping is recommended.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
2	For the following therapeutic targets - reverse transcriptase, protease, integrase - HIV DNA sequencing has a good positive predictive value (excluding APOBEC mutations) and an imperfect negative predictive value.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
3	In the context of a patient who has achieved virological success, in the event of a decision to reduce or simplify treatment to some long-acting regimens, prior genotyping on HIV DNA is useful for the clinical decision in the absence of usable or sufficiently informative RNA data.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
4	In a virologically suppressed patient, in the event of a decision to reduce or simplify to a sequential treatment (4 days out of 7 or 5 days out of 7) without changing any ARV agents, prior genotyping on HIV DNA is not essential for clinical decision-making, even in the absence of usable or sufficiently informative RNA data.	**Strong consensus**	Good consensus	**STRONG CONSENSUS**
5	In the absence of usable or sufficiently informative RNA data in a virologically suppressed patient, in the event of a decision to reduce/simplify to a treatment that reduces the number of ARV, prior genotyping on HIV DNA may be useful for clinical decision-making.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
Techniques for performing HIV DNA genotyping				
6	In current practice, when the amount of DNA is very low, the performance (sensitivity, representativeness of viral populations) of HIV DNA genotyping is reduced.	**Strong consensus**	N.A.	**STRONG CONSENSUS**
7	In current practice, genotyping on HIV DNA can be performed either from whole blood, from the cells isolated from peripheral blood (PBMC) or blood cell pellets.	**Strong consensus**	N.A.	**STRONG CONSENSUS**
8	Duplicate DNA genotyping increases performance (sensitivity, representativeness of viral populations) but is not possible in current clinical practice.	**Strong consensus**	N.A.	**STRONG CONSENSUS**
9	Sanger and ultra-deep sequencing can be used to perform HIV DNA genotyping.	**Strong consensus**	N.A.	**STRONG CONSENSUS**
10	For ultra-high throughput DNA sequencing techniques (ultra-deep sequencing), with the current state of knowledge, the clinically relevant detection threshold is not defined. Nevertheless, it may be interesting to report any viral minority population detected for multidisciplinary discussions.	**No Consensus**	N.A.	**NO CONSENSUS**
Consideration of APOBEC mutations				
11	Detection of the *M184I* mutation in HIV DNA is suggestive of the presence of a defective genome due to the APOBEC enzyme when it is associated with other suggestive mutations (e.g., *M41I, M230I* on reverse transcriptase) and/or stop codons.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
12	When resistance mutations attributable to APOBEC are detected, their significance should be interpreted with caution and based on the clinical context and treatment history.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
13	The presence of resistance mutations attributable to APOBEC should be reported in the HIV DNA genotyping analysis.	**Strong consensus**	N.A.	**STRONG CONSENSUS**
Reporting of genotyping results				
14	The clinical interpretation of resistance mutations on HIV DNA genotyping should be discussed at multidisciplinary consultation meetings.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
15	In a virologically suppressed patient, the detection on HIV DNA genotyping of new resistance mutations (excluding APOBEC & stop codons) previously undetected must be	**Strong consensus**	**Strong consensus**	**Strong consensus**

	considered for the treatment switch decision and subsequent follow-up.			
ARV recycling				
16	In a patient with an undetectable viral load for at least one year, in the presence of a documented M184V substitution over the past five years, the use of a 2nd generation InSTI + XTC + 1 NRTI combination presents **low risk** of virological failure over time.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
17	In a patient with an undetectable viral load for at least one year, in the presence of a documented M184V substitution over the past five years, the use of a 2nd generation InSTI + XTC combination **might present** a risk of virological failure over time.	**Strong consensus**	**No consensus**	**NO CONSENSUS**
18	The use / recycling of NNRTIs in the event of documented resistance to ARV agents of this class is associated with a greater risk of virological failure, independently of the duration of undetectable viral load, especially in drug-reduction strategies using ARV agents of this class.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
Test availability and delays				
19	HIV DNA genotypic tests should be accessible in clinical practice to all clinicians managing PLWH.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**
20	Reports of genotypic HIV DNA test results should be given to clinicians within 30 days.	**Strong consensus**	**Strong consensus**	**STRONG CONSENSUS**

N.A.: Not available; ARV: Antiretroviral; APOBEC: Apolipoproteins B mRNA editing enzyme; InSTI: Integrase Strand Transfer Inhibitor; XTC: Lamivudine/Emtricitabine; PLWH: People living with HIV.

Table S2 – Statements, detailed virologists' and clinicians' voting results, and cumulative results for both groups

For each statement, a total number of voters different from 21 for virologists and 40 or 47 for clinicians indicates the use of the 'I don't know' option by voters during the second voting round.

		VOTING SCORES FROM VIROLOGISTS					VOTING SCORES FROM CLINICIANS					CUMULATIVE SCORES
	STATEMENTS	**Scores 1-2-3 (n)**	**Scores 4-5-6 (n)**	**Scores 7-8-9 (n)**	**Median**	**Results**	**Scores 1-2-3 (n)**	**Scores 4-5-6 (n)**	**Scores 7-8-9 (n)**	**Median**	**Results**	
Clinical situations for the use of HIV DNA genotyping												
1	In the context of a therapeutic decision requiring genotyping data, when HIV RNA is not amplifiable, when cumulative HIV RNA genotyping is not available and/or or in the event of an incomplete or unusable genotypic history, HIV DNA genotyping is recommended.	4.8% (1)	0% (0)	95.2% (20)	9	**Strong consensus**	2.1% (1)	10.6% (5)	87.2% (41)	8	**Strong consensus**	**STRONG CONSENSUS**
2	For the following therapeutic targets - reverse transcriptase, protease, integrase - HIV DNA sequencing has a good positive predictive value (excluding APOBEC mutations) and an imperfect negative predictive value.	4.8% (1)	4.8% (1)	90.5% (19)	9	**Strong consensus**	2.1% (1)	17.0% (8)	80.9% (38)	8	**Strong consensus**	**STRONG CONSENSUS**
3	In the context of a patient with virological success, in the event of a decision to reduce or simplify treatment to some long-acting regimens, prior genotyping on HIV DNA is useful for clinical decision-making in the absence of usable or sufficiently informative RNA data.	9.5% (2)	4.8% (1)	85.7% (18)	9	**Strong consensus**	6.4% (3)	14.9% (7)	78.7% (37)	8	**Strong consensus**	**STRONG CONSENSUS**
4	In a virologically suppressed patient, in the event of a decision to reduce or simplify to a sequential treatment (4 days out of 7 or 5 days out of 7) without changing any ARV agents, prior genotyping on HIV DNA is not essential for the clinical decision, even in the absence of usable or sufficiently informative RNA data.	10% (2)	5% (1)	85.0% (17)	8	**Strong consensus**	15% (6)	12.5% (5)	72.5% (29)	8	Good consensus	**STRONG CONSENSUS**
5	In the absence of usable or sufficiently informative RNA data in a virologically suppressed patient, in the event of a desire to reduce/simplify towards a regimen that reduces the number of ARV agents prior genotyping on HIV DNA may be useful for clinical decision-making.	9.5% (2)	4.8% (1)	85.7% (18)	8	**Strong consensus**	7.5% (3)	17.5% (7)	75.0% (30)	8	**Strong consensus**	**STRONG CONSENSUS**
Techniques for performing HIV DNA genotyping												
6	In current practice, when the amount of DNA is very low, the performance (sensitivity, representativeness of viral populations) of HIV DNA genotyping is reduced.	5.3% (1)	5.3% (1)	89.5% (17)	9	**Strong consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	**STRONG CONSENSUS**
7	In current practice, genotyping on HIV DNA can be performed either from whole blood, from the cells isolated from peripheral blood (PBMC) or from blood	14.3% (3)	9.5% (2)	76.2% (16)	8	**Strong consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	**STRONG CONSENSUS**

	cell pellets.											
8	Duplicate DNA genotyping increases performance (sensitivity, representativeness of viral populations) but is not possible in current clinical practice.	10.5% (2)	5.3% (1)	84.2% (16)	8	**Strong consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	**STRONG CONSENSUS**
9	Sanger and ultra-deep sequencing can be used to perform HIV DNA genotyping.	0% (0)	23.8% (5)	76.2% (16)	8	**Strong consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	**STRONG CONSENSUS**
10	For ultra-high throughput DNA sequencing techniques (ultra-deep sequencing), with the current state of knowledge, the clinically relevant detection threshold is not defined. Nevertheless, it may be interesting to report to report any viral minority population detected for multidisciplinary discussions.	10% (2)	25% (5)	65% (13)	7.5	**No Consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	
Consideration of APOBEC mutations												
11	Detection of the *M184I* mutation in HIV DNA is suggestive of the presence of a defective genome due to the APOBEC enzyme when it is associated with other suggestive mutations (e.g., *M41I*, *M230I* on reverse transcriptase) and/or stop codons.	0% (0)	9.5% (2)	90.5% (19)	8	**Strong consensus**	3.1% (1)	15.6% (5)	81.3% (26)	8.5	**Strong consensus**	**STRONG CONSENSUS**
12	When resistance mutations attributable to APOBEC are detected, their significance should be interpreted with caution and based on the clinical context and treatment history.	4.8% (1)	0% (0)	95.2% (20)	9	**Strong consensus**	5.4% (2)	5.4% (2)	89.2% (33)	9	**Strong consensus**	**STRONG CONSENSUS**
13	The presence of resistance mutations attributable to APOBEC should be reported in the HIV DNA genotyping analysis.	9.5% (2)	4.8% (1)	85.7% (18)	8	**Strong consensus**	N.A.	N.A.	N.A.	N.A.	N.A.	**STRONG CONSENSUS**
Reporting of genotyping results												
14	The clinical interpretation of resistance mutations on HIV DNA genotyping should be discussed at multidisciplinary consultation meetings.	4.8% (1)	19% (4)	76.2% (16)	9	**Strong consensus**	4.8% (1)	19% (4)	76.2% (16)	9	**Strong consensus**	**STRONG CONSENSUS**
15	In a virologically suppressed patient, the detection on HIV DNA genotyping of new resistance mutations (excluding APOBEC & stop codons) previously undetected must be considered for a treatment switch decision and subsequent follow-up.	4.8% (1)	14.3% (3)	81% (17)	8	**Strong consensus**	4.8% (1)	14.3% (3)	81% (17)	8	**Strong consensus**	**STRONG CONSENSUS**
ARV recycling												
16	In a patient with an undetectable viral load for at least one year, in the presence of a documented M184V substitution over the past five years, the use of a 2nd generation InSTI + XTC + 1 NRTI combination presents low risk of virological failure over time.	14.3% (3)	9.5% (2)	76.2% (16)	8	**Strong consensus**	4.3% (2)	6.4% (3)	89.4% (42)	8	**Strong consensus**	**STRONG CONSENSUS**

17	In a patient with an undetectable viral load for at least one year, in the presence of a documented *M184V* substitution over the past five years, the use of a 2nd generation InSTI + XTC combination **might present** a risk of virological failure over time.	19% (4)	4.8% (1)	76.2% (16)	8	**Strong consensus**	22.5% (9)	25% (10)	52.5% (21)	7	**No consensus**	**NO CONSENSUS**
18	The use / recycling of NNRTIs in the event of documented resistance to ARV agents of this class is associated with a greater risk of virological failure, independently of the duration of undetectable viral load, especially in drug-reduction strategies using ARV agents of this class.	4.8% (1)	19% (4)	76.2% (16)	8	**Strong consensus**	0% (0)	17.9% (7)	82.1% (32)	8	**Strong consensus**	**STRONG CONSENSUS**
Test availability and delays												
19	HIV DNA genotypic tests should be accessible in clinical practice to all clinicians managing PLWH.	4.8% (1)	9.5% (2)	85.7% (18)	9	**Strong consensus**	10.6% (5)	6.4% (3)	83.0% (39)	9	**Strong consensus**	**STRONG CONSENSUS**
20	Reports of genotypic HIV DNA test results should be given to clinicians within 30 days.	4.8% (1)	4.8% (1)	90.5% (19)	9	**Strong consensus**	10.0% (4)	7.5% (3)	82.5% (33)	9	**Strong consensus**	**STRONG CONSENSUS**

N.A.: Not available; ARV: Antiretroviral; APOBEC: Apolipoproteins B mRNA editing enzyme; InSTI: Integrase Strand Transfer Inhibitor; XTC: Lamivudine/Emtricitabine; PLWH: People living with HIV

Table S3 – APOBEC context drug resistance mutations

ARV class	Major resistance mutations
PI	*M46I, G73S, D30N*
NRTI	*D67N, M184I*
NNRTI	*M230I, E138K, G190E, G190S*
InSTI	*G163R, G163K, G140R, D232N, E138K, G140S, G118R, R263K*

PI: Protease Inhibitor; InSTI: Integrase Strand Transfer Inhibitor