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

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30 **Abstract**

31 Objectives:

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

34 Methods:

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

39 Results:

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

53 Conclusion:

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

## 56 **1. Introduction**

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

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

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

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

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

## 82 **2. Material and methods**

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

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

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

### 101 *Steering Committee (SC)*

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

### 104 *Voting Group*

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

### 113 *Voting Round #1*

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

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

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

### 125 *Voting Round #2*

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

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

### 131 *Ethical considerations*

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

## 135 **3. Results**

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

### 141 *Participation*

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

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

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

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

#### 156 *Statements (Table 2)*

157 After Voting Round #1, 9/21 statements achieved a ‘strong’ consensus ( $\geq 75\%$  votes  $\geq 7$  and  
158 median  $\geq 8$ ); 5/21 statements achieved a ‘good’ consensus ( $\geq 75\%$  votes  $\geq 7$  or median  $\geq 8$ ) and  
159 7 statements lacked a consensus: 12 statements were revised by the SC for Voting Round #2,  
160 including all those which achieved a ‘good’ consensus and all those which did not achieve a  
161 consensus, of which two were merged resulting in 20 statements. After Voting Round #2,  
162 9/11 revised statements achieved a ‘strong’ consensus, and two statements did not achieve a  
163 consensus. In total, 18/20 statements (90%) achieved consensus. The distribution of  
164 cumulative votes, medians and results are provided in Table 2.

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

#### 168 Clinical situations for the use of HIV DNA genotyping

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

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



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

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

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

#### 186 Techniques for performing HIV-DNA genotyping

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

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

#### 200 Consideration of APOBEC mutations

201 The cytidine deaminases APOBEC3F and 3G enzymes might introduce G to A nucleotide  
202 mutations that can impair crucial enzymatic sites or generate stop codons that reduce the  
203 amount of replication competent proviruses.<sup>33-36</sup> Voters validated with a ‘strong’ consensus

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

#### 211 Reporting of genotyping results

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

#### 217 ARV recycling

218 Virologists and clinicians agreed with a ‘strong’ consensus that, in a patient with an  
219 undetectable viral load for at least one year and with documented *M184V* substitution on the  
220 current DNA genotype and/or on an RNA genotype performed within the last five years, the  
221 use of a 2<sup>nd</sup> generation InSTI (Integrase Strand Transfer Inhibitor) + XTC (Lamivudine or  
222 Emtricitabine) + 1 NRTI combination is at low risk of virological failure over time.  
223 Virologists validated with a ‘strong’ consensus that, under the same conditions, the use of a  
224 2<sup>nd</sup> generation InSTI + XTC combination may present a risk of virological failure over time.  
225 However, clinicians remained divided on this possible virological risk and their vote did not  
226 reach a consensus (‘no consensus’, no clinicians answered ‘I don't know’).

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

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

#### 232 Availability of HIV DNA genotyping tests and time to report results

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

#### 236 **4. Discussion**

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

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

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

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

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

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

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

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

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

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

309 virological failure over time.<sup>48</sup> 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 2<sup>nd</sup> generation InSTI + XTC  
312 regimen could present a risk of virological failure over time, as described in some literature.<sup>49</sup>  
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.<sup>50</sup>  
317 Since HIV DNA sequencing adds an important contribution to many clinical situations and  
318 patient follow-up,<sup>2</sup> 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.<sup>51</sup>  
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.<sup>52</sup> 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

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

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

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

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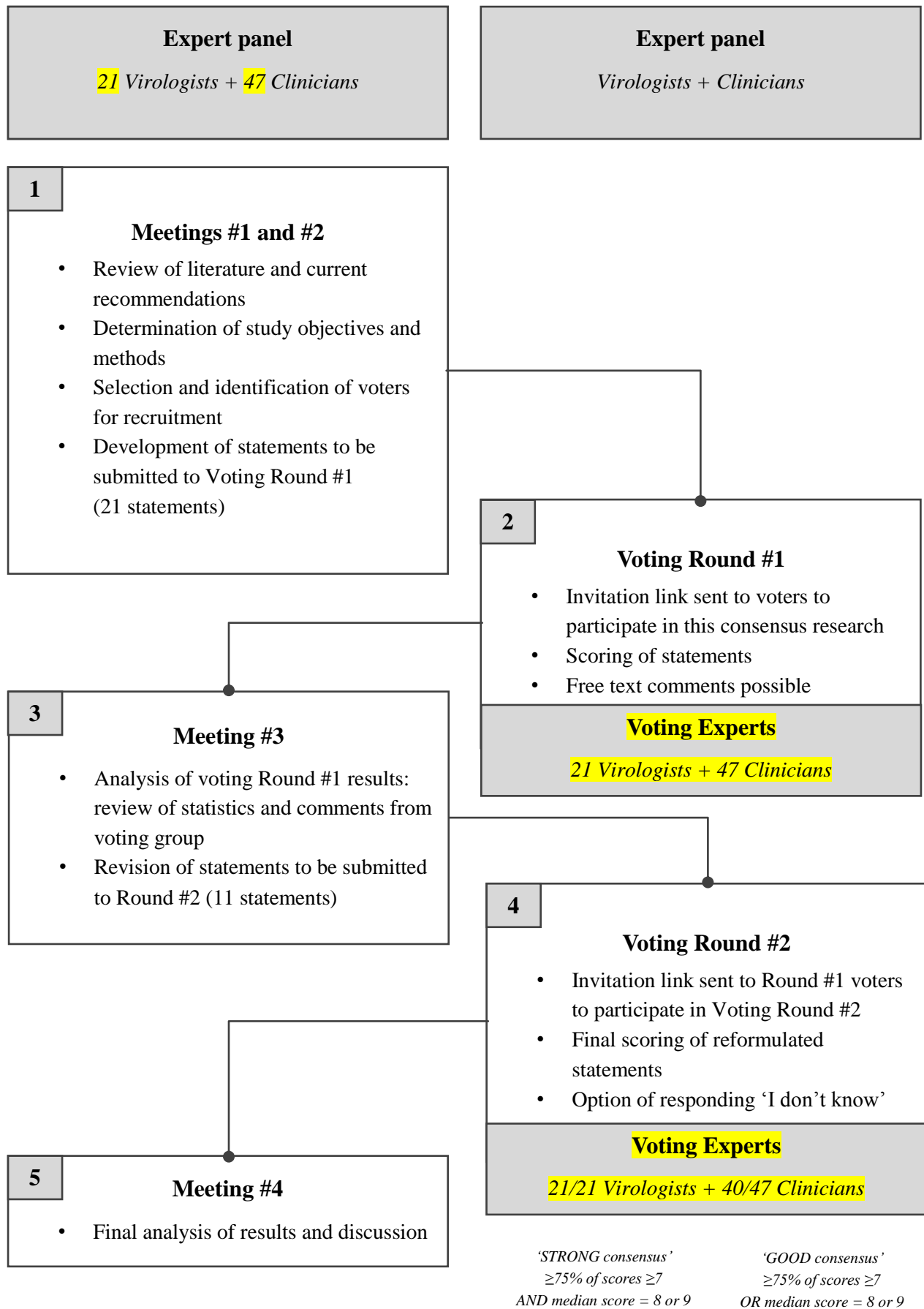
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**Figure 1: Modified Delphi process chart**





**Table 1 – Characteristics of voters**

<b>Characteristic</b>	<b>Virologists (n = 21)</b>	<b>Clinicians (n = 47)</b>
<b>Age, median [IQR], years</b>	46 [43-55]	56 [46-60.5]
<b>Gender F/M, n (%)</b>		
Female	16 (76)	18 (38)
Male	5 (24)	29 (62)
<b>Type of practice, n (%)</b>		
Full-time hospital workers	16 (76)	44 (94)
Part-time hospital workers	2 (10)	3 (6)
Others	3 (14)	-
<b>Years of experience performing HIV DNA sequencing, median [IQR], years</b>	10 [5-12]	-
<b>Number of HIV DNA genotypes performed per year, median [IQR]</b>	225 [42.5-425]	-
<b>Years of experience in PLWH management, median [IQR], years</b>	-	25 [15-31.5]
<b>Number of PLWH seen per year, median [IQR]</b>	-	270 [200-400]
<b>Experience in HIV care-related activities in the past 5 years, n (%)</b>		
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: deoxyribonucleic 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
<b>Clinical situations for the use of HIV DNA genotyping</b>						
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 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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
<b>Techniques for performing HIV DNA genotyping</b>						
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
9	Sanger and ultra-deep sequencing can be used to perform HIV DNA genotyping.	0% (0)	23.8% (5)	76.2% (16)	8	<b>Strong consensus</b>
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	<b>NO CONSENSUS</b>
<b>Consideration of APOBEC mutations</b>						
11	Detection of the <i>M184I</i> 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., <i>M41I</i> , <i>M230I</i> on reverse transcriptase) and/or stop codons.	1.9% (1)	13.2% (7)	84.9% (45)	8	<b>Strong consensus</b>
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>
<b>Reporting of genotyping results</b>						
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>

	switch decision and subsequent follow-up.					
<b>ARV recycling</b>						
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 2 <sup>nd</sup> generation InSTI + XTC + 1 NRTI combination presents <b>low risk</b> of virological failure over time.	7.4% (5)	7.4% (5)	85.3% (58)	8	<b>Strong consensus</b>
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 2 <sup>nd</sup> generation InSTI + XTC combination <b>might present</b> a risk of virological failure over time.	21.3% (13)	14.8% (9)	63.9% (39)	7	<b>NO CONSENSUS</b>
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	<b>Strong consensus</b>
<b>Test availability and delays</b>						
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	<b>Strong consensus</b>
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	<b>Strong consensus</b>

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
<b>Clinical situations for the use of HIV DNA genotyping</b>				
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 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
<b>Techniques for performing HIV DNA genotyping</b>				
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
<b>Consideration of APOBEC mutations</b>				
11	Detection of the <i>M184I</i> 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., <i>M41I</i> , <i>M230I</i> 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
<b>Reporting of genotyping results</b>				
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.			
<b>ARV recycling</b>				
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 2 <sup>nd</sup> generation InSTI + XTC + 1 NRTI combination presents <b>low risk</b> of virological failure over time.	<b>Strong consensus</b>	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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 2 <sup>nd</sup> generation InSTI + XTC combination <b>might present</b> a risk of virological failure over time.	<b>Strong consensus</b>	<b>No consensus</b>	<b>NO CONSENSUS</b>
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.	<b>Strong consensus</b>	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
<b>Test availability and delays</b>				
19	HIV DNA genotypic tests should be accessible in clinical practice to all clinicians managing PLWH.	<b>Strong consensus</b>	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
20	Reports of genotypic HIV DNA test results should be given to clinicians within 30 days.	<b>Strong consensus</b>	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>

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.



STATEMENTS		VOTING SCORES FROM VIROLOGISTS					VOTING SCORES FROM CLINICIANS					CUMULATIVE SCORES
		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	
<b>Clinical situations for the use of HIV DNA genotyping</b>												
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 in the event of an incomplete or unusable genotypic history, HIV DNA genotyping is recommended.	4.8% (1)	0% (0)	95.2% (20)	9	<b>Strong consensus</b>	2.1% (1)	10.6% (5)	87.2% (41)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	2.1% (1)	17.0% (8)	80.9% (38)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	6.4% (3)	14.9% (7)	78.7% (37)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	15% (6)	12.5% (5)	72.5% (29)	8	Good consensus	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	7.5% (3)	17.5% (7)	75.0% (30)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
<b>Techniques for performing HIV DNA genotyping</b>												
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	<b>Strong consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	<b>STRONG CONSENSUS</b>
7	In current practice, genotyping on HIV DNA can be performed either from whole blood, from the cells isolated from peripheral blood (PBMIC) or from blood	14.3% (3)	9.5% (2)	76.2% (16)	8	<b>Strong consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	<b>STRONG CONSENSUS</b>

	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	<b>Strong consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	<b>STRONG CONSENSUS</b>
9	Sanger and ultra-deep sequencing can be used to perform HIV DNA genotyping.	0% (0)	23.8% (5)	76.2% (16)	8	<b>Strong consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	<b>STRONG CONSENSUS</b>
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	<b>No Consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	
<b>Consideration of APOBEC mutations</b>												
11	Detection of the <i>M184I</i> 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., <i>M41I</i> , <i>M230I</i> on reverse transcriptase) and/or stop codons.	0% (0)	9.5% (2)	90.5% (19)	8	<b>Strong consensus</b>	3.1% (1)	15.6% (5)	81.3% (26)	8.5	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	5.4% (2)	5.4% (2)	89.2% (33)	9	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	N.A.	N.A.	N.A.	N.A.	N.A.	<b>STRONG CONSENSUS</b>
<b>Reporting of genotyping results</b>												
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	<b>Strong consensus</b>	4.8% (1)	19% (4)	76.2% (16)	9	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	4.8% (1)	14.3% (3)	81% (17)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
<b>ARV recycling</b>												
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 2 <sup>nd</sup> generation INSTI + XTC + 1 NRTI combination presents low risk of virological failure over time.	14.3% (3)	9.5% (2)	76.2% (16)	8	<b>Strong consensus</b>	4.3% (2)	6.4% (3)	89.4% (42)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>

17	In a patient with an undetectable viral load for at least one year, in the presence of a documented <i>M184V</i> substitution over the past five years, the use of a 2 <sup>nd</sup> generation InSTI + XTC combination <b>might present</b> a risk of virological failure over time.	19% (4)	4.8% (1)	76.2% (16)	8	<b>Strong consensus</b>	22.5% (9)	25% (10)	52.5% (21)	7	<b>No consensus</b>	<b>NO CONSENSUS</b>
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	<b>Strong consensus</b>	0% (0)	17.9% (7)	82.1% (32)	8	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
<b>Test availability and delays</b>												
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	<b>Strong consensus</b>	10.6% (5)	6.4% (3)	83.0% (39)	9	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>
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	<b>Strong consensus</b>	10.0% (4)	7.5% (3)	82.5% (33)	9	<b>Strong consensus</b>	<b>STRONG CONSENSUS</b>

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**

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

PI: Protease Inhibitor; InSTI: Integrase Strand Transfer Inhibitor