Optimizing HIV therapy. A consensus project on differences between cytidine analogues and regime compactness

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SUMMARY

Objectives. The identification of the most effective HAART regimens in different clinical settings is still an issue. The aim of the study was to analyze how the compactness of HAART regimens is perceived and if differences between lamivudine (3TC) and emtricitabine (FTC) do exist according to a panel of Italian HIV/AIDS clinicians, using the Delphi method.
Methods. The Delphi technique relies on a structured group of participants to reach a consensus on debated topics. Issues related to the compactness of HAART and to 3TC / FTC features were identified and proposed to randomly-selected 80 HIV/AIDS Italian clinicians by questionnaires. Questionnaires were administered in two rounds. The steering board of the project discussed the answers after each round to reformulate or to draw conclusions, respectively.
Results. Participants agreed that the compactness of HAART may influence adherence and outcome in many clinical conditions. Moreover, differences between FTC and 3TC were acknowledged with respect to pharmacokinetics, genetic barrier, antiviral potency, and resistance mutations arising at virologic failure.
Conclusions. The Delphi method proved useful to focus on and gauge the relevance of issues such differences between the two cytidine analogues (FTC and 3TC) and the overall compactness of HAART combinations in HIV/AIDS therapy.

KEY WORDS: HIV/AIDS therapy, HAART regimens, Compactness of regimens, Adherence, Persistence, Emtricitabine, Lamivudine, Delphi technique.

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INTRODUCTION

Since its inception, the use of highly active antiretroviral therapy (HAART) has been correlated with a substantial decrease in AIDS-defining conditions and their associated mortality (Thompson *et al.*, 2010). During the HAART era, the availability of new compounds has improved the effectiveness and reduced the toxicity of antiretroviral combinations; furthermore, new data on the timing of therapy initiation and on different regimen options continue to be generated (Thompson *et al.*, 2010; Hammer *et al.*, 2008).
Currently recommended ART regimens include three antiretroviral drugs: usually two nucleoside reverse transcriptase inhibitors (NRTI) plus a third agent, either a non-nucle-

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oside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI/r) or an INSTI (integrase strand-transfer inhibitor) (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013). As far as the NRTI backbone is concerned, the combination recommended by most guidelines is tenofovir (TDF) plus emtricitabine (FTC) - usually given as fixed-dose combination (FDC) - while other NRTIs such as abacavir (ABC), lamivudine (3TC) and zidovudine (ZDV) are mostly ranked as alternative choices (Thompson *et al.*, 2010; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013).

This different level of recommendation depends on differences among NRTIs in terms of antiviral potency, toxicity/tolerability profile, and chance of eliciting resistance-associated mutations (RAMs) at virologic failure (Gallant *et al.*, 2004; Pozniak *et al.*, 2006; Post *et al.*, 2010; Sax *et al.*, 2009). 3TC and FTC are often perceived as similar if not totally interchangeable molecules, while these two deoxy-cytidine analogues are reported to have some significant differences in pharmacokinetic properties, antiviral activity and RAM emergence at failure (Frampton and Perry, 2005; Rousseau *et al.*, 2003; Svicher *et al.*, 2010; Drogan *et al.*, 2010). Another pivotal issue relating to the choice between 3TC and FTC is the current availability of FTC within two FDCs, one - as mentioned above - with TDF only (Truvada®) and the other with both TDF/FTC and EFV (Atripla®) (Maserati *et al.*, 2010), while 3TC is co-formulated with abacavir or zidovudine. Since more compact and simpler combinations have been associated with a better adherence and enhanced long-term virologic and immunological success (Willig *et al.*, 2008; Ross *et al.*, 2006; Palacios *et al.*, 2009), mostly by using once-a-day, single-tablet regimens (Moyle, 2003; Airoldi *et al.*, 2010; Stone *et al.*, 2004; Ortego *et al.*, 2011), it is interesting to gauge how much importance caregivers place on the compactness of an antiretroviral regimen in different clinical situations. The aim of this study is to measure the degree of consensus on two issues in antiretroviral therapy (compactness of a combination and differences between 3TC and FTC) among a large group Italian HIV/AIDS clinical experts by using the Delphi Technique.

METHODS

The Delphi Technique is a validated process to develop consensus and make group-based decisions in a variety of fields (Turoff and Hiltz, 1995). It was conceived and developed in the mid-1950s by researchers at the Rand Corporation as a way to predict the impact of technologies or interventions on complex systems, and has often been used in the social and health care context (Linstone and Turoff, 1975; Adler and Ziglio, 1996; Graham *et al.*, 2003).

The Delphi method is traditionally based on three fundamental concepts, as shown in figure 1. The first is *anonymity*. The participants never meet each other during the process. Each participant submits his or her opinions independently, by completing a specially designed questionnaire. The replies are then disclosed to all participants, without identifying the particular respondent. The second concept is *controlled feedback*. The process consists of several rounds; during each of them the respondents are asked to judge all the opinions expressed in the previous rounds, often presented in the form of statistics. The last concept is *statistical group response*. The Delphi method reaches a collective opinion or a collective decision and expresses it in terms of a statistical score.

In addition to these basic characteristics, the Delphi method can be described as follows:

- It requires *individual effort* for the expression of an opinion.
- It requires *written answers* to questionnaires.
- The *individual opinions* (questionnaire responses) are collected and assembled by the project coordinator.
- The respondents have *enough time* to come up with and evaluate opinions (unlike task force meetings, in which, quite often, not enough time is allowed to assess other people's opinions).

Consensus techniques in general (Thompson *et al.*, 2010; Hammer *et al.*, 2008) and the Delphi method in particular (Scheer *et al.*, 2009) have been used specifically in the field of HIV/AIDS for epidemiological, inhabitant awareness and behavioural research.

For the purpose of this project, a steering committee (comprised of seven persons widely recognized as authorities on HIV/AIDS and work-

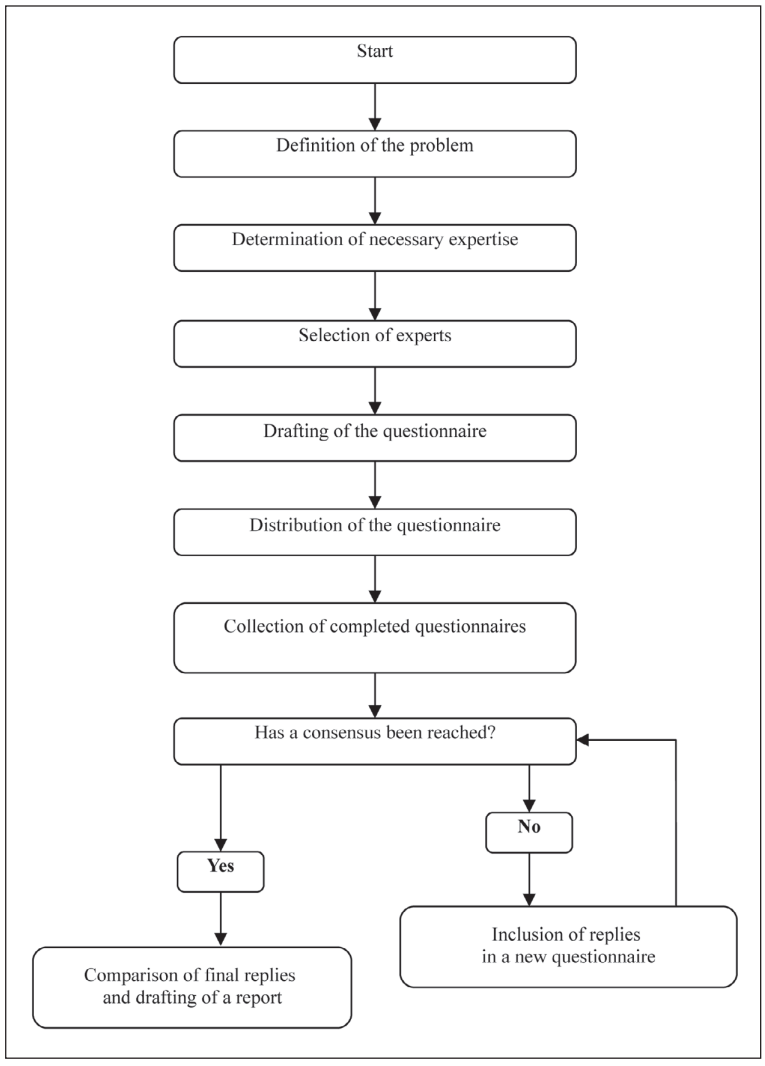

FIGURE 1 - *Phases of the Delphi method.*

ing in Italian universities, public hospitals, and private institutions) examined the scientific literature and developed a 23-item questionnaire (Q1; see Table 1). The questionnaire was designed to be submitted to an expert panel of HIV/AIDS specialists. These individuals (from here on called "experts") were randomly selected among MDs directly involved in the care of HIV/AIDS patients. Criteria for entering this random selection were a robust expertise in treating patients (more than 10 uninterrupted years of clinical work in this field and no less than 300 HIV/AIDS patients personally followed at the time of the project start) and the consent to undergo the Delphi procedure used in the project. A particular effort was made to cover in the most uniform and comprehensive way different clinical practices across Italy by enrolling in the project caregivers from all the three main geographic regions (north, centre, south). In Q1 the sequence of questions followed no apparent logic, to avoid any inadvertent influence that might cause bias. For each question, space was provided for comments.
The majority of Q1 questions allowed graded answers on a scale of 0 to 5 (Table 1).
After the replies to Q1 were processed, a second questionnaire (Q2) was developed. Q2 was presented to the same expert panel and replies were collected and processed in the same way.
To better analyze the replies to Q1 and Q2, two categories of answers were defined:

- Score of 0-2: negative answer;
- Score of 3-5: positive answer.

After both rounds, the level of agreement was evaluated based on the percentage of positive and negative answers to each question. To reach consensus, a cut-off level of two-thirds (or 66%) agreement was required either for the first (Q1) and the second round (Q2). All members of the steering committee agreed on this arbitrary but standard consensus level before the study began.

RESULTS

An expert panel of 80 HIV/AIDS specialists was identified in the three different regions of Italy, as stated in the "Methods" paragraph. When the project was actually put into effect, we were able to recruit 72 respondents (90% of those initially selected), whose geographical breakout was befitting our purpose of enrolling MDs from northern (46%), central (32%) and southern (22%) Italy. Q2 was sent to the 72 respondents to Q1, and 62 (86% of them) returned an answer. The percentage of respondents choosing each reply is presented in Tables 1 and 2.

By analyzing the replies to both questionnaires, the board identified the following statements about ART that attained expert agreement of two thirds or more:

1. The compactness of an antiretroviral regimen means both a *restricted pill burden* and a *reduced number of administrations per day* (such as QD vs. bid) (Q2, 1); this factor may impact adherence to treatment (Q1, 1-2), by curbing the risk of selective adherence (intended as failing to take one or more treatment components) (Q2, 9), and the short- to medium/long-term outcome (Q1, 3-4).
2. Features like "compactness" and "co-formulation" may be relevant to the prescribing physician (Q1, 7) and to the patient (Q1, 9) in choosing between 3TC and FTC in clinical practice (Q2, 23-24). According to the expert panel, differences between these two drugs do exist (Q1, 5), though the toxicity/tolerability profiles of 3TC and FTC are almost the same (Q1, 6).
3. The compactness of an antiretroviral regimen has a significant effect on treatment adherence *in the short term:* in naïve, late-presenter patients (Q2, 2); in asymptomatic patients with high CD4+ T cell count (Q2, 3); in multi-treated patients (Q2, 4); in chronically-infected, virologically-suppressed patients (Q2, 5). The same effect on adherence *in the medium/long term* was gauged: in naïve patients (irrespective of baseline clinical presentation) (Q2, 6); in multi-treated patients (Q2, 7); and in chronically-infected, virologically-suppressed patients (Q2, 8).
4. An easier HAART treatment helps achieve greater *persistence of the regimen* in both naïve and experienced patients (Q2, 13-14), but HAART persistence is an important parameter for experienced patients only (Q2, 12) and not for naïve ones (Q2, 11).
5. There are convincing data on differences in *antiviral potency* between 3TC and FTC (Q1, 8 and Q2, 20). Moreover, the *genetic barrier* of an antiretroviral regimen may influence the treatment outcome in the medium/long term (Q1, 12) but not in the short term (Q1, 11). Most notably, 3TC and FTC display a different genetic barrier to the emergence of RAMs (Q1, 13), and this parameter should influence the choice between these two drugs (Q2, 21). The *resistance profiles* of 3TC and FTC show significant differences in case of virologic failure (Q2, 22), with a different risk also of leading to the emergence of NNRTI-associated RAMs (Q1, 15).
6. The *pharmacokinetic "symmetry"* of an antiretroviral regimen (intended as the broad equivalence of the compounds' plasma and/or intracellular half-lives) may be pivotal for the treatment outcome (Q1, 17). In the case of FTC, TDF and EFV - when co-formulated in a FDC - it may influence the prescribing physician's choice in the daily clinical practice between FTC and 3TC (Q2, 25). This was associated to some pharmacokinetic properties (Q1, 18) deemed to be significantly different between the two compounds such as: a. plasma half-life; b. intracellular half-life (triphosphate metabolite); c. substrate (reverse transcriptase) affinity; d. activity in functional mono-therapy; e. combinations of all the above (Q2, 19 a-e).
7. The antiretroviral *penetration into reservoirs*

turned out to be of paramount importance in the treatment of asymptomatic patients (Q1, 19), and particularly for patients with neurological symptoms or signs (Q1, 20). Therefore, a different neuro-penetration score (Letendre *et al.*, 2008) may influence the choice between 3TC and FTC (Q1, 21; Q2, 26).

8. When selecting the first antiretroviral treatment, the most important patient characteristics are level of immune-deficiency (number and percentage of CD4+ T lymphocytes), presence of co-morbidities and level of HIV RNA viremia (Q1, 10).
9. From the prescribing physician viewpoint, the three most important factors in the choice of an antiretroviral treatment for *naïve, late-presenter patients* were identified in: antiviral potency, tolerability and ability to trigger an immune recovery (Q2, 15). When asked the same question for *asymptomatic patients with high CD4+ T cell count*, the key factors were: tolerability, adherence, and – with a tied score – compactness and antiviral potency (Q2, 16), while in *multi-treated patients with high CD4+ T cell count* the choice banked on antiviral potency, genetic barrier and tolerability (Q2, 17). Finally, when *considering switching therapy in chronically-infected, virologically-suppressed patients*, the experts settled on tolerability, compactness and adherence as the most valuable elements for the ideal HAART combination to use (Q2, 18).
10. In clinical practice, the prescribing physician does not differentiate between brand name medications and generics containing a similar active compound (Q1, 22). Moreover, clinicians do not consider the price of an antiretroviral regimen when choosing between 3TC and FTC (Q2, 10), but do not accept an excessive (as vaguely as it may be defined) increased cost of a co-formulated medication compared with the single components administered separately (Q1, 23).

DISCUSSION AND CONCLUSIONS

While the current HAART era still enjoys a relative plenty of active compounds that can be mixed in a variety of combinations, no general agreement has been reached on what could be defined as the "optimal" association of drugs, should one exist for all patients (Gallant, 2004). Even in a relatively simple clinical situation such as the treatment of naïve patients without baseline RAMs, the most authoritative guidelines still leave a variety of options (Hammer *et al.*, 2008; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013), based on what the prescriber may think is more relevant for the individual patient about to start treatment. However, one issue that seems to have emerged over the last few years as being of utmost importance in guiding the initial therapy (and also, if feasible, in later stages of treatment) is the compactness of the HAART regimen (Airoldi *et al.*, 2010). A more compact regimen usually means a better adherence that, in turn, dictates a steady and dependable antiviral activity. A persistent HIV RNA suppression in plasma is the main goal to be reached with HAART and the cornerstone to immunologic recovery (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013).

Another key point in this field is to realize how similar and how different some compounds belonging to the same class of antivirals may be. While some contrasts have been readily and widely perceived (first generation vs. second generation PIs; thymidine vs. non-thymidine NRTIs), others may not be so clearly acknowledged and misperceptions still linger in the caregiver community.

The opinions expressed by the experts in Questionnaires 1 and 2 can be summarized as follows:

• Experts strongly agreed on the definition of compactness as meaning a limited number of pills and also a limited number of administrations per day (Q2, 1). They also shared the opinion that a regimen should be tailored to each patient to enhance adherence and thus improve treatment success in the short and in the medium/long term either (Q1, 1-4). In this regard, compactness is an important characteristic of an antiretroviral regimen (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013). A systematic review in the non-HIV literature have shown that adherence is inversely related to the number of daily doses

(Claxton *et al.*, 2001). Some prospective studies in HIV-infected individuals have shown that patients placed on regimens with reduced dosing frequency have higher levels of adherence (Gallant *et al.*, 2006; Molina *et al.*, 2007). Patient satisfaction index with regimens that contain fewer pills and reduced dosing frequency is also higher (Stone *et al.*, 2004). These findings are supported by the two questionnaires, in which the relationship between compactness and adherence was deemed significant in both the short and the medium/long term for all types of patients (naïve, asymptomatic with high CD4+ T cell count, multi-treated, chronically-infected, virologically-suppressed) (Q2, 2-8). A simple switch to FDC may induced a sharp increase in adherence levels, as demonstrated in a study by an Italian group of investigators (Airoldi *et al.*, 2010). This substantiates the importance of both co-formulation and compactness for prescribing physicians (Q1, 7) and for patients (Q1, 9), highlighting the difference between FTC and 3TC (Q2, 23,24).

• Unlike adherence, persistence is a longitudinal measure of how valuable an antiretroviral therapy may be, emphasizing continuity rather than frequency. "Undemanding" regimens with fewer drugs, FDCs, newer generations of NRTIs, boosted-protease inhibitors, and efavirenz may heighten the regimen persistence both in naïve (Q2, 13) and in experienced (Q2, 14) patients (Baea *et al.*, 2011). However, in this study persistence was not regarded as a significant parameter for naïve patients (Q2, 11), while it was deemed to be significant in experienced individuals (Q2, 12). This concept may be more pertinent in developed countries, where there is a wide choice of initial antiretroviral regimens in naïve patients thanks to the high availability of drugs with a great likelihood of reaching virological suppression with most of them. Compared to the initial regimen, the second and the third treatment initiated because of virological failure are significantly less likely to achieve an undetectable viral load (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Willig *et al.*, 2008). Furthermore, each modification is associated with a more complex dosing schedule, a less favorable toxicity profile, and decreased persistence of the subsequent regimen. Therefore, the persistence parameter is very important for experienced patients.

• Despite the structural similarities between emtricitabine (FTC) and lamivudine (3TC), the panel agreed on differences in their antiviral potency (Q2, 20) with regard to antiretroviral activity in functional monotherapy, substrate affinity, and pharmacokinetic (PK) properties including a longer intracellular half-life of active triphosphate metabolite (Q2, 19 a-d) (Rousseau *et al.*, 2003; Drogan *et al.*, 2010). In addition to these issues, a different genetic barrier has been found in recent studies (Svicher *et al.*, 2010; Maserati *et al.*, 2010; Marcelin *et al.*, 2011), with a significantly lower prevalence of M184V/I mutations (Q2, 22) in a failing FTC/TDF/EFV regimen compared with patients failing 3TC/TDF/EFV. This consideration may influence the prescriber's choice (Q1, 13-14; Q2, 21). Moreover, 3TC-containing regimens seem to be associated with a greater probability of eliciting NNRTI-associated RAMs at virologic failure (Q1, 15) (Maserati *et al.*, 2010). As far as "pharmacokinetic symmetry" is concerned, FTC was judged to show a substantial homogeneity of plasma and/or intracellular half-life with those of TDF and EFV compared with 3TC (Q1, 17; Q2, 25). Indeed, this characteristic was evaluated and validated in the FOTO study, concerning the safety of a two-day break on FTC/TDF/EFV-based antiretroviral therapy (Cohen *et al.*, 2008). As for neuro-penetration, the CNS penetration-effectiveness score (CPE score) has been proposed to define the efficacy of an antiretroviral regimen in CNS (Letendre *et al.*, 2008). A high CPE score has been deemed to be associated with a lesser amount of HIV RNA in cerebrospinal fluid and with better neurocognitive performance, particularly in patients with neurological symptoms (Q1, 19-21; Q2, 26) (Tozzi *et al.*, 2009).

• As far as the choice of an antiretroviral regimen is concerned, the most important features should reflect the goals included in international and national guidelines for the use of antiretroviral agents according to type of patient (Q2, 15-18) (Thompson *et al.*, 2010; Hammer *et al.*, 2008; Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013; Antinori *et al.*, 2011). Because tolerability is a common objective for physicians prescribing antiretroviral

therapy (Airoldi *et al*., 2010), the expert panel agreed on maximizing efficacy, safety, and quality of life for HIV-positive patients.

• Another point of interest is the increased cost of a co-formulated medication. FDCs are easier to manage - for both patients and health workers - because they increase adherence, thereby reducing the possibility of functional monotherapy in situations of selective non-compliance and of developing HIV resistance to antiretrovirals. More than 80% of clinicians agreed to sustain a limited cost increase for FDCs (up to 20%) (Q1, 23), because drug resistance could influence future treatment options of individual patients increasing expenditure and complexity. A failing regimen may also lead to HIV transmission and originate a public health concern. On the other hand, due to a shrinking budget and economic restraints that may be more pronounced in certain geographical areas, physicians may accept generic medication containing compounds similar to the brand name product (Q1, 22). Considering the global, ongoing financial crisis and a likely curtailing of the funds devoted to antiretrovirals, the panel endorsed the proposal that as soon as all components of currently available FDCs become available as generics, they should be developed into generic FDCs (Llibre *et al*., 2011).

The Delphi method has advantages and drawbacks.

On the positive side, it can overcome many of the limitations intrinsic to traditional group decision-making processes, keeps attention directly on the issue, and is flexible and inexpensive compared with, say, the focus group. Depending on the nature of the problem, the method can be adjusted for improved overall efficacy. For example, since the use of strict statistical methods for setting guidelines is rather problematic, due to the qualitative nature of the expected result, the use of modified classification procedures makes it easier to monitor and express the process by which a consensus is developed.

As for the disadvantages, information comes from a selected group of people and may not be representative; there is a tendency to eliminate extreme positions and force a middle-of-the-road consensus; it is more time-consuming than group process methods; and it requires skill in written communication, as well as adequate time and participant commitment.

Ultimately, the consensus building process has become part of the technique for solving problems in health and medicine, by putting the knowledge and experience of practitioners and other experts in touch with the scientific literature.

In conclusion, in different clinical situations (such as naive vs. experienced patients or in AIDS-presenters vs. asymptomatic individuals), the expert panel responses suggested some key features for constructing an ideal HIV treatment regimen.

The relationship between compactness, adherence and persistence of the HAART, irrespective of the time window considered, was strongly highlighted by the panel.

The ideal NRTI backbone should be convenient, safe and tolerable, show a durable activity and preserve future therapeutic options if virological failure occurs. No single NRTI backbone has properties making it ideal for every patient, but each one has advantages and disadvantages.

Even though FTC and 3TC are considered similar compounds by many physicians, a convincing consensus has been established on the differences between FTC and 3TC with regard to antiviral potency, genetic barrier, RAMs at virological failure, and pharmacological and pharmacokinetic profiles.

The majority of the panel takes these differences into account when prescribing a new treatment, either for suppression of a replicating virus or for simplification purposes in patients with an undetectable plasma viral load.

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TABLE 1 - *Questionnaire 1 - Answers are expressed as percentage of all responses. Cut-off level to reach consensus: two-thirds (66.66%) agreement of effective answers.*

Question	*% Each option*	*% Combined options (0,1,2 / 3,4,5)*	*Consensus*
1. How much may the compactness of an antiretroviral regimen influence treatment adherence in the short term?			Yes
0 lowest influence	1.41%	18.31%	
1	7.04%		
2	9.86%		
3	38.03%	81.69%	
4	26.76%		
5 greatest influence	16.90%		
2. How much may the compactness of an antiretroviral regimen influence treatment adherence in the medium/long term?			Yes
0 lowest influence	0.00%	2.78%	
1	1.39%		
2	1.39%		
3	13.89%	97.22%	
4	54.17%		
5 greatest influence	29.17%		
3. How much may the compactness of an antiretroviral regimen influence treatment outcome in the short term?			Yes
0 lowest influence	1.39%	27.78%	
1	11.11%		
2	15.28%		
3	40.28%	72.22%	
4	22.22%		
5 greatest influence	9.72%		
4. How much may the compactness of an antiretroviral regimen influence treatment outcome in the medium/long term?			Yes
0 lowest influence	0.00%	7.04%	
1	2.82%		
2	4.23%		
3	22.54%	92.96%	
4	47.89%		
5 greatest influence	22.54%		
5. How much do you agree with the statement "There are significant differences between lamivudine (3TC) and emtricitabine (FTC)"?			Yes
0 lowest agreement	0.00%	27.78%	
1	16.67%		
2	11.11%		
3	37.50%	72.22%	
4	27.78%		
5 greatest agreement	6.94%		

→

Question	*% Each option*	*% Combined options (0,1,2 / 3,4,5)*	*Consensus*
6. How much do you agree with the statement "Toxicity / tolerability profiles of lamivudine (3TC) and emtricitabine (FTC) are almost the same"?			Yes
0 lowest agreement	0.00%	8.33%	
1	2.78%		
2	5.56%		
3	26.39%	91.67%	
4	41.67%		
5 greatest agreement	23.61%		
7. How much may "compactness" and "co-formulation" influence the prescribing physician's choice between 3TC or FTC in clinical practice?			Yes
0 lowest influence	1.43%	4.29%	
1	1.43%		
2	1.43%		
3	14.29%	95.71%	
4	58.57%		
5 greatest influence	22.86%		
8. How tenable are the data in favour of a different antiviral potency between 3TC or FTC?			Yes
0 least	4.41%	26.47%	
1	13.24%		
2	8.82%		
3	42.65%	73.53%	
4	19.12%		
5 greatest	11.76%		
9. How much may "compactness" and "co-formulation" influence the patient's choice between 3TC or FTC in clinical practice?			Yes
0 lowest influence	2.78%	15.28%	
1	5.56%		
2	6.94%		
3	26.39%	84.72%	
4	40.28%		
5 greatest influence	18.06%		
10. What are the most important characteristics impacting on patients' choice when considering the first antiretroviral regimen? (rank in order of importance from 1 to 6)	Score +	Rank	
a. Lifestyle	193	4	
b. Age	151	5	
c. Gender	96	6	
d. Co-morbidity	271	2	
e. Immune deficiency	285	1	
f. Viremia	243	3	

→

Question	*% Each option*	*% Combined options (0,1,2 / 3,4,5)*	*Consensus*
11. How much may the genetic barrier of an antiretroviral regimen influence treatment outcome in the short term?			No
0 lowest influence	1.41%	33.80%	
1	9.86%		
2	22.54%		
3	22.54%	66.20%	
4	33.80%		
5 greatest influence	9.86%		
12. How much may the genetic barrier of antiretroviral regimen influence treatment outcome in the medium/long term?			Yes
0 lowest influence	1.41%	11.27%	
1	0.00%		
2	9.86%		
3	8.45%	88.73%	
4	47.89%		
5 greatest influence	32.39%		
13. Do you think there is convincing evidence of a different genetic barrier to drug resistance between 3TC and FTC?			Yes
a. Yes	76.06%		
b. No	23.94%		
14. How much may the genetic barrier influence the physician's choice between 3TC or FTC in clinical practice?			Yes
0 lowest influence	6.94%	33.33%	
1	13.89%		
2	12.50%		
3	23.61%	66.67%	
4	31.94%		
5 greatest influence	11.11%		
15. How important is it that 3TC and FTC have been associated with a different risk of emerging NNRTI-linked RAMs at treatment failure?			Yes
0 lowest importance	4.23%	23.94%	
1	11.27%		
2	8.45%		
3	28.17%	76.06%	
4	29.58%		
5 greatest importance	18.31%		
16. How relevant are the pharmacokinetics of antiretrovirals in influencing the treatment outcome in the short term?			Yes
0 lowest influence	1.39%	15.28%	
1	2.78%		
2	11.11%		
3	30.56%	84.72%	
4	41.67%		
5 greatest influence	12.50%		

→

Question	*% Each option*	*% Combined options (0,1,2 / 3,4,5)*	*Consensus*
17. How important is pharmacologic "symmetry" (intended as the broad equivalence of the compounds' half-lives) for treatment outcome?			Yes
0 lowest influence	1.41%	11.27%	
1	4.23%		
2	5.63%		
3	19.72%	88.73%	
4	50.70%		
5 greatest influence	18.31%		
18. How much may pharmacokinetics influence the prescribing physician's choice between 3TC or FTC?			Yes
0 lowest influence	7.04%	32.39%	
1	14.08%		
2	11.27%		
3	22.54%	67.61%	
4	36.62%		
5 greatest influence	8.45%		
19. How much may the penetration of antiretrovirals into reservoirs be relevant in the treatment of asymptomatic patients?			Yes
0 lowest relevance	1.39%	11.11%	
1	4.17%		
2	5.56%		
3	20.83%	88.89%	
4	44.44%		
5 greatest relevance	23.61%		
20. How important is the neuro-penetration of antiretrovirals in the treatment of patients with neurological symptoms or signs?			Yes
0 lowest importance	0.00%	2.78%	
1	0.00%		
2	2.78%		
3	1.39%	97.22%	
4	23.61%		
5 greatest importance	72.22%		
21. To what extent do you think neuro-penetration data may influence the physician's choice between 3TC or FTC in clinical practice?			Yes
0 lowest influence	1.39%	29.17%	
1	12.50%		
2	15.28%		
3	19.44%	70.83%	
4	36.11%		
5 greatest influence	15.28%		

→

Question	*% Each option*	*% Combined options (0,1,2 / 3,4,5)*	*Consensus*
22. To what extent would the choice between a brand name medication and a generic containing a similar compound influence clinical practice?			No
0 lowest influence	9.72%	34.72%	
1	5.56%		
2	19.44%		
3	22.22%	65.28%	
4	27.78%		
5 greatest influence	15.28%		
23. To what extent would you sustain the increased cost of a co-formulated medication (with added value in terms of better convenience and adherence) compared with the single components administered separately?			
a. Nothing	21.13%		
b. Up to a further 10%	38.03%		
c. Up to a further 20%	26.76%		
d. Up to a further 30%	7.04%		
e. Up to a further 50%	7.04%		

TABLE 2 - *Questionnaire 2 - Answers are expressed as percentage of all responses. Cut-off level to reach consensus: two-thirds (66.66%) agreement of effective answers.*

Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
1. How would you define the "compactness" of an antiretroviral regimen?			Yes
a. a limited number of pills per day (for example 1 vs. 3)	3.28%		
b. a limited number of administrations per day (for ex. QD vs. bid)	1.64%		
c. both of the above	95.08%		
2. To what extent does the compactness of an antiretroviral regimen influence adherence in naïve, late-presenter patients in the short term?			Yes
0 lowest influence	0.00%	27.12%	
1	15.25%		
2	11.86%		
3	35.59%	72.88%	
4	25.42%		
5 greatest influence	11.86%		
3. To what extent does the compactness of an antiretroviral regimen influence adherence in asymptomatic patients with high CD4+ T cell count in the short term?			Yes
0 lowest influence	0.00%	8.33%	
1	1.67%		
2	6.67%		
3	23.33%	91.67%	
4	50.00%		
5 greatest influence	18.33%		
4. To what extent does the compactness of an antiretroviral regimen influence adherence in multi-treated patients in the short term?			Yes
0 lowest influence	1.64%	29.51%	
1	11.48%		
2	16.39%		
3	32.79%	70.49%	
4	29.51%		
5 greatest influence	8.20%		
5. To what extent does the compactness of an antiretroviral regimen influence adherence in chronically-infected, virologically-suppressed patients in the short term?			Yes
0 lowest influence	0.00%	9.84%	
1	3.28%		
2	6.56%		
3	34.43%	90.16%	
4	32.79%		
5 greatest influence	22.95%		

→

Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
6. To what extent does the compactness of an antiretroviral regimen influence adherence in naïve patients in the medium/ long term (irrespective of baseline conditions)?			Yes
Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
0 lowest influence	0.00%	8.20%	
1	0.00%		
2	8.20%		
3	21.31%	91.80%	
4	45.90%		
5 greatest influence	24.59%		
7. To what extent does the compactness of an antiretroviral regimen influence adherence in multi-treated patients in the medium/long term?			Yes
0 lowest influence	0.00%	21.31%	
1	6.56%		
2	14.75%		
3	36.07%	78.69%	
4	27.87%		
5 greatest influence	14.75%		
8. To what extent does the compactness of an antiretroviral regimen influence adherence in chronically-infected, virologically-suppressed patients with chronic infection in the medium-long term?			Yes
0 lowest influence	0.00%	5.00%	
1	0.00%		
2	5.00%		
3	23.33%	95.00%	
4	40.00%		
5 greatest influence	31.67%		
9. The compactness of an antiretroviral regimen may lower the risk of selective adherence (intended as the failed intake of one or more components of the regimen)			Yes
0 lowest agreement	0.00%	8.47%	
1	1.69%		
2	6.78%		
3	11.86%	91.53%	
4	45.76%		
5 greatest agreement	33.90%		

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Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
10. Currently, to what extent does the price of an antiretroviral regimen influence your choice between 3TC and FTC?			No
0 lowest influence	6.67%	41.67%	
1	15.00%		
2	20.00%		
3	35.00%	58.33%	
4	11.67%		
5 greatest influence	11.67%		
11. The "persistence" of an antiretroviral regimen (intended as maintaining the initial HAART over time) is an important parameter for naive patients.			No
0 lowest agreement	4.84%	35.48%	
1	14.52%		
2	16.13%		
3	29.03%	64.52%	
4	20.97%		
5 greatest agreement	14.52%		
12. HAART persistence is an important parameter for experienced patients.			Yes
0 lowest agreement	3.23%	27.42%	
1	8.06%		
2	16.13%		
3	27.42%	72.58%	
4	30.65%		
5 greatest agreement	14.52%		
13. A higher degree of persistence is associated with simplified regimens in naive patients.			Yes
0 lowest agreement	1.64%	11.48%	
1	1.64%		
2	8.20%		
3	16.39%	88.52%	
4	47.54%		
5 greatest agreement	24.59%		
14. A higher degree of persistence is associated with simplified regimens in experienced patients.			Yes
0 lowest agreement	0.00%	21.67%	
1	1.67%		
2	20.00%		
3	35.00%	78.33%	
4	25.00%		
5 greatest agreement	18.33%		
15. What do you think are the most important characteristics in the choice of an antiretroviral regimen in naïve, late-presenter patients? (rank in order of importance from 1 to 9)	Score +	Rank	
a. Compactness	371	6	
b. Adherence	322	5	

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Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
c. Pharmacokinetic symmetry	201	7	
d. Price	106	9	
e. Co-formulation	176	8	
f. Genetic barrier	358	4	
g. Antiviral potency	497	1	
h. Tolerability	406	2	
i. Immune recovery	395	3	
16. What do you think are the most important characteristics in the choice of an antiretroviral regimen in asymptomatic patients with high CD4+ T cell count? (rank in order of importance from 1 to 9)	Score +	Rank	
a. Compactness	371	3	
b. Adherence	406	2	
c. Pharmacokinetic symmetry	207	7	
d. Price	186	8	
e. Co-formulation	250	6	
f. Genetic barrier	329	5	
g. Antiviral potency	371	3	
h. Tolerability	424	1	
i. Immune recovery	142	9	
17. What do you think are the most important characteristics in the choice of an antiretroviral regimen in multi-treated patients? (rank in order of importance from 1 to 9)	Score +	Rank	
a. Compactness	235	6	
b. Adherence	314	5	
c. Pharmacokinetic symmetry	196	7	
d. Price	100	9	
e. Co-formulation	177	8	
f. Genetic barrier	456	2	
g. Antiviral potency	499	1	
h. Tolerability	365	3	
i. Immune recovery	335	4	
18. What do you think are the most important characteristics in the choice of an antiretroviral regimen when switching therapies in chronically infected, virologically-suppressed patients? (rank in order of importance from 1 to 9)	Score +	Rank	
a. Compactness	407	2	
b. Adherence	396	3	
c. Pharmacokinetic symmetry	212	7	
d. Price	200	8	
e. Co-formulation	324	4	
f. Genetic barrier	261	5	
g. Antiviral potency	258	6	
h. Tolerability	423	1	
i. Immune recovery	141	9	

→

Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
19. FTC and 3TC show significant differences for the parameters listed below: (express your agreement with this statement for each parameter) a. Plasma half-life			Yes
0 lowest agreement	3.39%	11.86%	
1	5.08%		
2	3.39%		
3	23.73%	88.14%	
4	42.37%		
5 greatest agreement	22.03%		
19. b. Intracellular half-life (triphosphate metabolites)			Yes
0 lowest agreement	0.00%	5.26%	
1	0.00%		
2	5.26%		
3	24.56%	94.74%	
4	35.09%		
5 greatest agreement	35.09%		
19. c. Substrate (reverse transcriptase) affinity			Yes
0 lowest agreement	3.45%	24.14%	
1	5.17%		
2	15.52%		
3	34.48%	75.86%	
4	27.59%		
5 greatest agreement	13.79%		
19. d. Activity in functional monotherapy			Yes
0 lowest agreement	8.62%	27.59%	
1	6.90%		
2	12.07%		
3	34.48%	72.41%	
4	29.31%		
5 greatest agreement	8.62%		
19. e. Combinations of all of the above parameters			Yes
0 lowest agreement	0.00%	13.56%	
1	3.39%		
2	10.17%		
3	28.81%	86.44%	
4	38.98%		
5 greatest agreement	18.64%		
20. The antiviral potencies of 3TC and FTC are significantly different.			Yes
0 lowest agreement	0.00%	32.76%	
1	10.34%		
2	22.41%		
3	29.31%	67.24%	
4	32.76%		
5 greatest agreement	5.17%		

→

Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
21. The genetic barrier may influence your choice between 3TC and FTC.			Yes
0 lowest agreement	0.00%	25.00%	
1	11.67%		
2	13.33%		
3	35.00%	75.00%	
4	30.00%		
5 greatest agreement	10.00%		
22. When choosing between 3TC and FTC, how relevant is a different resistance profile between the two compounds in case of virologic failure ?			Yes
0 lowest relevance	3.33%	26.67%	
1	6.67%		
2	16.67%		
3	31.67%	73.33%	
4	26.67%		
5 greatest relevance	15.00%		
23. "Compactness" and "co-formulation" may influence your choice between 3TC and FTC.			Yes
0 lowest agreement	0.00%	11.67%	
1	6.67%		
2	5.00%		
3	23.33%	88.33%	
4	41.67%		
5 greatest agreement	23.33%		
24. Do you believe that "compactness" and "co-formulation" are more relevant for you or for your patients, when selecting 3TC or FTC?			
patient	45.90%		
physician	54.10%		
25. To what extent does the "pharmacokinetic symmetry" (intended as homogeneous plasma and/or intracellular half-lives) of FTC, TDF and EFV formulated as FDC influence the choice between FTC and 3TC?			Yes
0 lowest influence	0.00%	14.75%	
1	6.56%		
2	8.20%		
3	29.51%	85.25%	
4	32.79%		
5 greatest influence	22.95%		

→

Question	*% each option*	*% combined options (0,1,2 / 3,4,5)*	*Consensus*
26. To what extent do data on neuro-penetration influence your choice between FTC and 3TC?			Yes
0 lowest influence	0.00%	21.31%	
1	6.56%		
2	14.75%		
3	29.51%	78.69%	
4	37.70%		
5 greatest influence	11.48%		

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