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Antiretroviral treatment French guidelines 2013: economics influencing science

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Guidelines for the preferred choice of initial combination antiretroviral therapy in those living with HIV are provided by several national and international committees. Following the recent presentation of the 2013 French guidelines on antiretroviral therapy, there has been a debate regarding whether and/or how economics should influence guideline decisions and to what extent this should counterbalance valid scientific evidence. We discuss here the reasons for the unique nature of some of the proposals made by the French guidelines panel. Indeed, some recommendations are debatable. In the new French guidelines, economic considerations significantly influence and, in some instances, take precedence over the scientific evidence, leading to guidelines that are significantly different from those of other national and international committees.

Keywords: ART, antiretroviral therapy, preferred regimens, high-income countries, cost-effectiveness

The 2013 French guidelines on HIV therapy were released at the end of September 2013.[1] Many of the recommendations conflict with scientific evidence. Economic considerations influencing proposed choices can cause confusion, as it is not always clear whether the guidelines are for the public health authorities to change the current framework of HIV care or recommendations for best practice. Indeed, the new French guidelines are unique—a true 'French paradox'—and differ in many respects from those from all high-resource countries [IAS-USA Panel, Department of Health and Human Services (DHHS) US Panel, European, British, Italian and Spanish].[2–8] Such differences reflect a different approach and methodology. Traditionally, treatment guidelines have been based almost entirely on reviews of the available evidence and expert opinion. Members of the working groups conduct extensive and unbiased literature reviews to identify relevant new information, then analyse and synthesize the information obtained—grading the evidence and the strength of evidence—and make recommendations that are then voted upon.[9,10] This approach is the one used by the guidelines committees of the DHHS, IAS-USA, Italian, Spanish and European AIDS Clinical Society (EACS) groups. The British HIV Association (BHIVA) committee uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considered as even more rigorous.[6,11] In France, recommendations are made by members of each group as illustrated in this article, grading and strength of evidence being determined *a posteriori*. Such a process means the recommendations are influenced by economic considerations and are not purely science driven. It is not the medical evidence that is the basis for the proposal but rather the proposal finds support in evidence that includes financial factors.[10]

The consideration of cost in making guideline decisions has been a major element for low-income countries, as for WHO guidelines, but this has in the past led to the promotion of therapies that are less than optimal or even toxic, such as nevirapine, stavudine or zidovudine. The influence of economics in making guideline decisions is also worthy of debate in Western countries; however, economic considerations should include not only the cost of drug acquisition but also resource utilization costs, which include the cost of laboratory monitoring tests (related to toxicity), the cost of additional clinical visits due to tolerability issues and of additional medications needed for managing side effects, the cost of managing virological failure and of treatment modification, and other indirect costs, which vary according to drugs and regimens. Cost-effectiveness models have been used to evaluate the impact of earlier treatment on the cost of care[12] and of treatments as prevention strategies.[13] There are no available data on cost-effectiveness evaluations of different first-line antiretroviral regimens, which could be used as a factor in the decision-making process for preferred versus alternative regimens, or how costs could balance or diminish scientific evidence. The French panel has included the cost of drugs as a factor without taking into consideration full cost-effectiveness, offering a new way to make recommendations. However when economics drives decision making, considering only drug costs can lead to bias. This might lead to 'atypical' recommendations, as illustrated by the new French guidelines (Table 1).

The best example is the recommendation for first-line antiretroviral therapy. In the 2013 guidelines, the recent data on the superiority of triple therapies containing an integrase strand-transfer inhibitor, and their long-term benefit with low toxicity and a high retention rate with low treatment discontinuation, are not

Table 1. Preferred recommended first-line antiretroviral regimens in countries with high-income resources[a]

	BHIVA[6] (04/2012)	IAS-USA[2] (07/2012)	France[1] (09/2013)	EACS[5] (10/2013)	DHHS[3,4] (30/10/2013)
TDF/FTC/EFV	yes	yes	yes	yes	yes
TDF/FTC/RPV	—	—	yes	yes	no
TDF/FTC+ATV/RTV	yes	yes	yes	yes	yes
TDF/FTC+DRV/RTV	yes	yes	yes	yes	yes
TDF/FTC+RAL	yes	yes	no	yes	yes
TDF/FTC/EVG/CBS	—	—	no	no	yes
TDF/FTC+DTG	—	—	no	no	yes
ABC/3TC+EFV	no	yes	yes	yes	no
ABC/3TC+RPV	—	—	no	yes	no
ABC/3TC+ATV/RTV	no	yes	yes	yes	no
ABC/3TC+DRV/RTV	no	no	no	yes	no
ABC/3TC+RAL	no	no	no	yes	no
ABC/3TC+DTG	—	—	no	—	yes

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; RPV, rilpivirine; ATV, atazanavir; RTV, ritonavir; DRV, darunavir; RAL, raltegravir; EVG, elvitegravir; CBS, cobicistat; DTG, dolutegravir; ABC, abacavir; 3TC, lamivudine.
[a]The comparison of recommendations of guidelines issued in 2012 and 2013 needs great caution, as data for newer drugs have only recently become available or granted approval (this is reflected by instances of '—' in the table).

incorporated. Indeed, in contrast to all other high-resource countries' guidelines, which list raltegravir-based regimens as one of the preferred first-line options, with a rating of 'A1', French guidelines do not have raltegravir as a preferred first-line treatment but rather list raltegravir-based regimens as alternatives, with a 'B1' grading. This French exception (Table 1) raises the possibility that this difference could be linked to two factors. The first is that group members did not consider the data on 5 year outcomes for raltegravir compared with efavirenz therapy in the first head-to-head, fully powered, double-blind, class comparison study on which the non-French recommendations are based.[14] The second factor is that taking into account the acquisition costs of antiretrovirals leads to a downgraded recommendation of a major antiretroviral, the only one commercially available in France to have demonstrated superiority over another class and that is not associated, in contrast to other preferred drugs, with lack of efficacy in a subgroup of patients (rilpivirine) or with significant long-term toxicity (efavirenz, ritonavir-boosted protease inhibitors). Therefore, if the cost of drugs is one of the driving elements of decision making, without taking into account the indirect costs associated with virological failure and its management or with intolerance or toxicity, then it would have been logical to list in the preferred options nevirapine, which is one of the cheapest antiretrovirals to date.[1,5] Continuing to propose tenofovir/emtricitabine/efavirenz as a choice equal to other preferred first-line options in mid-2013 does not constitute a treatment strategy advance and does not reflect the most recent evidence, since three large Phase III studies show its inferiority compared with raltegravir or dolutegravir,[14,15] or to rilpivirine in patients with a baseline viral load <100 000 copies/mL.[16] If one wishes to include medico-economic criteria in the rating of different antiretroviral regimens, this should include not only the acquisition costs of drugs but also all direct and indirect costs associated with a given strategy. This includes long-term data comparing the efficacy and safety of different strategies in head-to-head clinical trials and also long-term real-life epidemiological data, such as those showing the clear superiority of integrase strand-transfer inhibitor-based regimens[14,15] and the low frequency of treatment change or discontinuation for safety or toxicity problems compared with historically preferred options (i.e. efavirenz or atazanavir/ritonavir).[17]

Another proposal in the 2013 French guidelines is to encourage the prescription and dispensing of generic HIV drugs. The guidelines propose to 'replace Atripla® by the combination of generic efavirenz plus generic lamivudine+tenofovir (Viread®)... with the intake of 3 pills instead of 1, and substitution of lamivudine for emtricitabine, whose activity is equivalent' (page 103). This proposal, with a genuine economic perspective, ignores the simplification of therapy strategy that has been promoted by HIV experts (and is favoured by patients) to improve acceptability, convenience and long-term adherence. Most importantly, the statement that lamivudine and emtricitabine are equivalent is inadequate, as five independent studies comparing both nucleoside reverse transcriptase inhibitors (NRTIs) show that, compared with emtricitabine, lamivudine is associated with significantly lower virological efficacy and a higher prevalence of emergence of resistance to lamivudine and associated antiretrovirals.[18–22] The introduction of an economic criterion for choice of therapy could lead to the intentional selection of antiretroviral combinations with potentially lower efficacy and/or poorer convenience or tolerability.

To reconcile scientific and economic aspects, it would have been possible to propose only one preferred first-line treatment option, the tenofovir/emtricitabine/rilpivirine single-tablet regimen (or abacavir/lamivudine+rilpivirine) in eligible patients (those with viral load <100 000 copies/mL and without baseline rilpivirine-associated mutations), who represent 75% of naive patients and the quasi-totality of virologically suppressed patients who could benefit from treatment simplification. For treatment-naive patients with high pre-treatment viral load, the choice

could have then been more open, with either a ritonavir-boosted protease inhibitor-based regimen or an integrase strand-transfer inhibitor-based regimen, to favour potency and rapidity of control of viral load.

With regard to the management of virologically suppressed patients, a frequent clinical situation, French guidelines state that 'Several randomized clinical trials have demonstrated the efficacy of such a strategy, i.e. switching ritonavir-boosted protease inhibitor to non-nucleoside reverse transcriptase inhibitor, with efavirenz or nevirapine' with little reference to the evidence. There is only one (and not several) randomized trial, which concerns efavirenz and that actually shows non-inferiority with respect to the substitution of efavirenz for a ritonavir-boosted protease inhibitor.[23] When dealing with the switch of a ritonavir-boosted protease inhibitor to raltegravir, the SPIRAL study, which has been the subject of five publications in international journals during the period 2010–13, is not discussed or even cited.[24–28] There is only a brief mention of the DEXA sub-study in the lipodystrophy section of the guidelines.[25] A critical review of these five papers shows the potential benefit of the ritonavir-boosted protease inhibitor–raltegravir switch beyond virological endpoint, with improvement in lipids, metabolic parameters, and bone and also inflammatory markers, this latter point also being evidenced in an independent study of enfuvirtide–raltegravir switch—the EASIER/ANRS 148 trial.[29]

In the section on simplification to ritonavir-boosted protease inhibitor monotherapy, although criteria associated with the success of such a strategy are clearly indicated, the recommendation remains vague, 'can be discussed on a case-by-case basis', in spite of the fact that this strategy could lead to a substantial economic benefit. Thus, there is uncertainty in how to proceed (does case-by-case mean in every case or in exceptional situations?) and no clear guidelines are proposed. The US guidelines ('boosted-protease inhibitor monotherapy as simplification treatment has been somewhat less effective in achieving complete virological suppression and avoiding resistance. Therefore, this strategy cannot be recommended outside of a clinical trial')[3] or the European guidelines ('ritonavir-boosted protease inhibitor monotherapy might represent an option in patients with intolerance to NRTI or for treatment simplification')[5] make different recommendations but are much more straightforward and precise on what to do. If long-term data on switch strategy for ritonavir-boosted protease inhibitor monotherapy had been reviewed and considered, such as the 3 year MONET trial data),[30] the economic benefit, without virological risk, of their strategy could have been raised. With the bottom-line perspective of French guidelines to reduce the cost of antiretroviral therapy, the absence of clear guidelines on simplification with lopinavir/ritonavir or darunavir/ritonavir monotherapy is intriguing.

The proposal for post-exposure prophylaxis is also confusing. Indeed, it is stated that 'Among ritonavir-boosted protease inhibitor, lopinavir/ritonavir 2 pills twice daily in combination with tenofovir/emtricitabine is the most used combination, but gastro-intestinal side effects are frequent. Atazanavir/ritonavir … (87% hyperbilirubinemia and 66% of clinical jaundice). Darunavir/ritonavir has not been evaluated in this situation…', with the following conclusion: 'Thus, lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir can be prescribed as first options.' It is difficult to follow the reasoning for ranking darunavir/ritonavir or atazanavir/ritonavir at the same level as lopinavir/ritonavir when two-thirds of patients develop hyperbilirubinaemia or clinical icterus when taking atazanavir/ritonavir and with no data for darunavir/ritonavir. Furthermore, raltegravir is not recommended 'owing to its cost', without any reference to, or discussion of, the two concordant published studies that show the greater convenience and tolerability of raltegravir + tenofovir/emtricitabine compared with the previous standard of lopinavir/ritonavir + tenofovir/emtricitabine.[31,32] The panel does not allude to the work, submitted in July 2013 and presented by a French group at the 2013 EACS conference, showing that tenofovir/emtricitabine plus raltegravir is much better tolerated than other regimens used for post-exposure prophylaxis and, as stated in the abstract, 'might be considered as a new standard post-exposure prophylaxis drug regimen'.[33]

Indeed, a critical review of the available evidence should lead to the recommendation of tenofovir/emtricitabine + raltegravir for occupational exposures, as in the new US guidelines, issued on 6 August 2013.[34]

In conclusion, the new 2013 French guidelines on HIV therapy are controversial, as they are not always based on the latest evidence-based data. Rating evidence in treatment guidelines should remain based on strict methodology and rigorous evaluation of data from randomized controlled trials, and on extensive review of the latest literature. The wish to incorporate economic criteria when making recommendations and therapeutic choices should neither mask the scientific evidence nor lead to a loss of opportunity for persons living with HIV.

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