Which antiretrovirals should be prescribed as first-line treatments? Changes over the past 10 years in France

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Quels antirétroviraux en première ligne ? Évolution en France au cours des 10 dernières années.

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Mots clés : inhibiteurs d'intégrase, traitement antirétroviral initial, infection par le VIH

Keywords: initial HIV therapy; integrase strand transfer inhibitors; HIV infection

Résumé

Objectif. Décrire les choix de premier traitement antirétroviral en France entre 2005 et 2015 et analyser les caractéristiques liées à l'utilisation d'inhibiteurs de protéase (IP) en 2015.

Méthodes. Tous les patients ayant débuté leur traitement entre le 01/01/2005 et le 31/12/2015 et suivis dans la cohorte Dat'AIDS ont été inclus. Les schémas thérapeutiques ont été classés comme suit : trois analogues nucléosidiques (NRTI), deux NRTI avec un IP boosté (IPb), avec un analogue non nucléosidique (NNRTI), ou avec un inhibiteur de l'intégrase (INSTI). Les caractéristiques des patients à l'instauration du traitement ont été recueillies. Un modèle multinomial a été construit afin d'analyser les caractéristiques liées à la prescription d'IPb en 2015.

Résultats. 15 897 patients analysés. La proportion de patients recevant un IPb est passée de 60 % avant 2014 à 38,1 % en 2015 et celle recevant un NNRTI a diminué de 30 % à 17,8 % en 2015. L'utilisation d'INSTI a progressivement augmenté jusqu'à 39,4 % en 2015. En 2015, les patients ayant une charge virale > 5 log/ml recevaient moins souvent un NNRTI (OR=0,08) ou un INSTI (OR=0,69) qu'un IPb. Les patients ayant moins de 200 CD4/mm^3 recevaient moins souvent un NNRTI (OR=0,28) ou un INSTI (OR=0,52) qu'un IPb. Les femmes recevaient moins souvent un NNRTI (OR=0,79) ou un INSTI (OR=0,71) qu'un IPb, cela dépendait aussi de leur âge.

Conclusion. L'utilisation d'IPb a significativement diminué au cours de la dernière décennie, mais reste préférée en cas de CD4 bas, de charge virale élevée ou chez les femmes.

Abstract

Objective. To describe the changes in first-line antiretroviral (ART) regimens in France between 2005 and 2015 and patients' characteristics related to the use of protease inhibitors in 2015.

Methods. We extracted all patients starting ART between 2005 and 2015 from a large prospective cohort. Regimens were classified as three nucleoside reverse transcriptase inhibitors (NRTI), or two NRTIs with a boosted protease inhibitor (bPI), with a non-nucleoside reverse transcriptase inhibitor (NNRTI), or with an INSTI. Patients' characteristics at the time of initiation were collected. A multinomial logit model was fitted to analyze characteristics related to the choice of regimen in 2015.

Results. We analyzed data from 15,897 patients. The proportion of patients starting with *(i)* a bPI decreased from 60% before 2014 to 38.1% in 2015; *(ii)* an NNRTI decreased from 30% to 17.8% in 2015; *(iii)* an INSTI gradually increased to 39.4% in 2015. In 2015, patients with an initial viral load >5 log copies/ml were less likely to receive NNRTI (OR=0.08) or INSTI regimens (OR=0.69) than bPIs. Patients with initial $CD4^+$ T cell count <200/mm^3 were less likely to receive an NNRTI (OR=0.28) or an INSTI regimen (OR=0.52) than a bPI. Women were less likely to receive an NNRTI (OR=0.79) or an INSTI regimen (OR=0.71) than a bPI; although this depended on age.

Conclusion. The use of bPI as first-line ART declined sharply in France from 2005 to 2015. bPI remained of preferential use in patients with high viral load, low $CD4^+$ T cell count, and in women.

Introduction

The best first-line antiretroviral treatment (ART) has been disputed since the introduction of effective treatments for patients presenting with human immunodeficiency virus (HIV) infection, and guidelines are in constant evolution [1, 2]. Protease inhibitors − usually ritonavir-boosted (bPI) − have long been the preferred choice in France [3]. Integrase inhibitors (INSTIs) have been available in France since 2009 and recommended as first-line treatments since 2014 [4]. On the basis of a large prospective cohort of patients managed in France, we aimed to describe the changes in recommended first-line treatments observed between 2005 and 2015 and to analyze the characteristics of patients for whom bPIs were still the best treatment choice in 2015.

Patients and method

Patients included in the Dat'AIDS cohort, based on data from the computerized medical chart known as Nadis® [5], managed in 16 facilities of metropolitan France and overseas territories were included in the analysis if their first ART had been prescribed between January 1, 2005 and December 31, 2015. The 16 facilities were spread over the whole territory: three in Paris, four in the North East of France (Tourcoing, Strasbourg, Besançon, Nancy), two overseas (Guadeloupe and Martinique), four in the South of France (Montpellier, Toulouse, Marseille, Nice), one in Nantes, and two in the Rhône-Alpes region (Lyon and Clermont-Ferrand). Treatments were defined as three nucleoside reverse transcriptase inhibitor analogues (NRTI), or two NRTIs with a bPI, with a non-nucleoside reverse transcriptase inhibitors (NNRTI) or with an INSTI. Other treatment regimens were classified as "other". We analyzed the patient's age, the acquisition mode of HIV, $CD4^+$ T cells, HIV viral load, and the presence of a co-infection with the hepatitis B or C viruses at the time of ART initiation.

Qualitative variables were described as frequency and compared by year of ART initiation using a Chi-square test. Quantitative variables were described as median and interquartile range and were compared by year using the non-parametric Kruskal Wallis test. A multinomial logistic regression was used to analyze the characteristics related to the choice of first-line treatment. Considering the high

interaction between the patients' gender and the acquisition mode of HIV, these variables were combined for the multivariate analysis to create a three-category new variables: men who have sex with men (MSM, N=659), women (N=377), and heterosexual men (N=406).

Given the historical preference for bPIs (Table 1), the other treatment protocols were compared with the bPI-based regimen (Figure 1). As women of childbearing potential may require a different treatment, the multivariate analysis was secondarily performed using the sole group of women.

Results

We included 15,897 patients in the analysis. Their characteristics at the time of treatment initiation are detailed in Table 1. The proportion of men increased from 62.7% to 73.8% (p<0.001) between 2005 and 2015. The median age at treatment initiation remained stable (38 years old) for the whole population, but it decreased in men and increased in women (p<0.001 in both cases). The proportion of patients infected with HIV through intravenous drug use decreased over the years (from 4.8% to 2%), just like the proportion of patients infected during heterosexual intercourse (from 54.2% to 42.3%). Conversely, the proportion of infections contracted by men who have sex with men increased from 30.3% in 2005 to 46.1% in 2015 (global p<0.001). The proportion of patients presenting with an hepatitis B or C coinfection decreased from 16.4% in 2005 to 9.4% in 2015 (p<0.001). We observed a progressive increase in $CD4^+$ T cell levels at the time of treatment initiation, from a median of 232 in 2005 to 390 cells/mm^3 in 2015 (p<0.001), while the HIV viral load remained stable (4.7 $\log_{10}$ copies/ml).

Changes in first-line ART are also detailed in Table 1. The proportion of patients receiving a first-line bPI treatment decreased from 61.8% in 2005 to 44.2% in 2014 (year when INSTIs were recommended as first-line treatments) and then to 38.1% in 2015. A decreased use of first-line NNRTIs was then observed, from approximately 30% before 2015 to 17.8% in 2015. Conversely, the proportion of patients receiving a first-line treatment with an INSTI, which was around 5% when this drug class was available but not recommended as first-line treatment, increased to 39% in 2015.

The multivariate analysis revealed that among patients started on ART in 2015, those with an initial viral load >5 log_{10} copies/ml were less frequently treated with an NNRTI (OR=0.08, 95% CI [0.05-0.14]) or an INSTI (OR=0.69 [0.54-0.89]) than with a bPI; patients with $CD4^+$ T cell levels <200 cells/mm^3 were less frequently treated with an NNRTI (OR=0.28 [0.19-0.42]) or an INSTI (OR=0.42 [0.32-0.58]) than with a bPI; and women less frequently received an INSTI (OR=0.71 [0.53-0.97]) than a bPI or an NNRTI (OR=0.79 [0.53-1.17]) than a bPI. The other initial characteristics did not impact the likelihood of receiving one ART over another in 2015. Findings from the multivariate analysis restricted to women revealed that $CD4^+$ T cells and viral load were unchanged, but that the likelihood of using a bPI decreased with age (Figure 1).

Discussion

We reported marked changes in prescribing habits of first-line ART in France over the past 10 years, i.e. protease inhibitors are less frequently used and integrase inhibitors are more frequently prescribed. The efficacy and tolerability of raltegravir has been established in 2007, and the drug is associated with a higher proportion of patients with an undetectable viral load than efavirenz [6]. Raltegravir was launched in 2009 in France, as two daily doses. It was recommended as a first-line treatment in 2014 only. Cobicistat-boosted elvitegravir was shown to be as effective as boosted atazanavir [7] or as efavirenz [8]. First-line dolutegravir was associated with a higher efficacy than boosted darunavir [9], raltegravir [10], and efavirenz [11]. It is also well-tolerated. Dolutegravir and elvitegravir have been available in France since early 2014 as single tablets combined with two NRTIs, as a daily dose. It should be noted that only a small proportion of patients received these molecules as soon as data was published and drugs available, but before their recommendation as first-line treatments in the national guidelines. As French physicians are known for following guidelines [12], changes in prescribing habits were therefore expected as early as the beginning of the year 2014. Our data confirms this hypothesis.

Patients with a high initial viral load and those with low $CD4^+$ T cell levels were still very likely to receive a first-line bPI in 2015. As this group of patients is mainly made of patients with delayed screening and diagnosis, the physicians' trust in bPIs − based on years of experience − may encourage them not to change their prescribing habits with these patients. Conversely, this group of patients may also include patients managed at the acute phase of the infection − and bPIs were still recommended as first-line treatments in this context in 2015. Women were also highly likely to receive a first-line bPI; we may hypothesize that this is due to a potential pregnancy. Women's decreasing likelihood of receiving a bPI with age may support this hypothesis.

Strengths of our study are its sample size and the prospective data collection. However, it also has limitations. The initial treatment choice is based on various parameters, which could not be taken into account in our analysis. Physicians may assess the risk of non-compliance, and thus decide to start with a bPI to prevent the emergence of resistance mutations. However, one must note that the price of drugs is usually not an obstacle in the choice of one molecule over another as all drugs are entirely reimbursed.

Conclusion

INSTI availability significantly changed the first-line ART choice in France. Scientific data on the use of INSTI in patients with late diagnosis of primary infection or in pregnant women could lead to even more significant changes.

Acknowledgments

P.P. and L. Cuzin defined the analysis plan. V. J., M.A.V, L. Cotte, T. H., C.A, J.R, I. P-M, and F. B-S controlled the quality of data. L. Cuzin wrote the article. All authors reviewed and approved the final version of the article.

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Figure 1. Probabilité de recevoir un ART en 2015 en fonction du genre, des CD4 et de la charge virale, et effet de l'âge chez les femmes

Figure 1. Likelihood of receiving an ART in 2015 by sex, CD4 cell count, viral load, and impact of women's age.

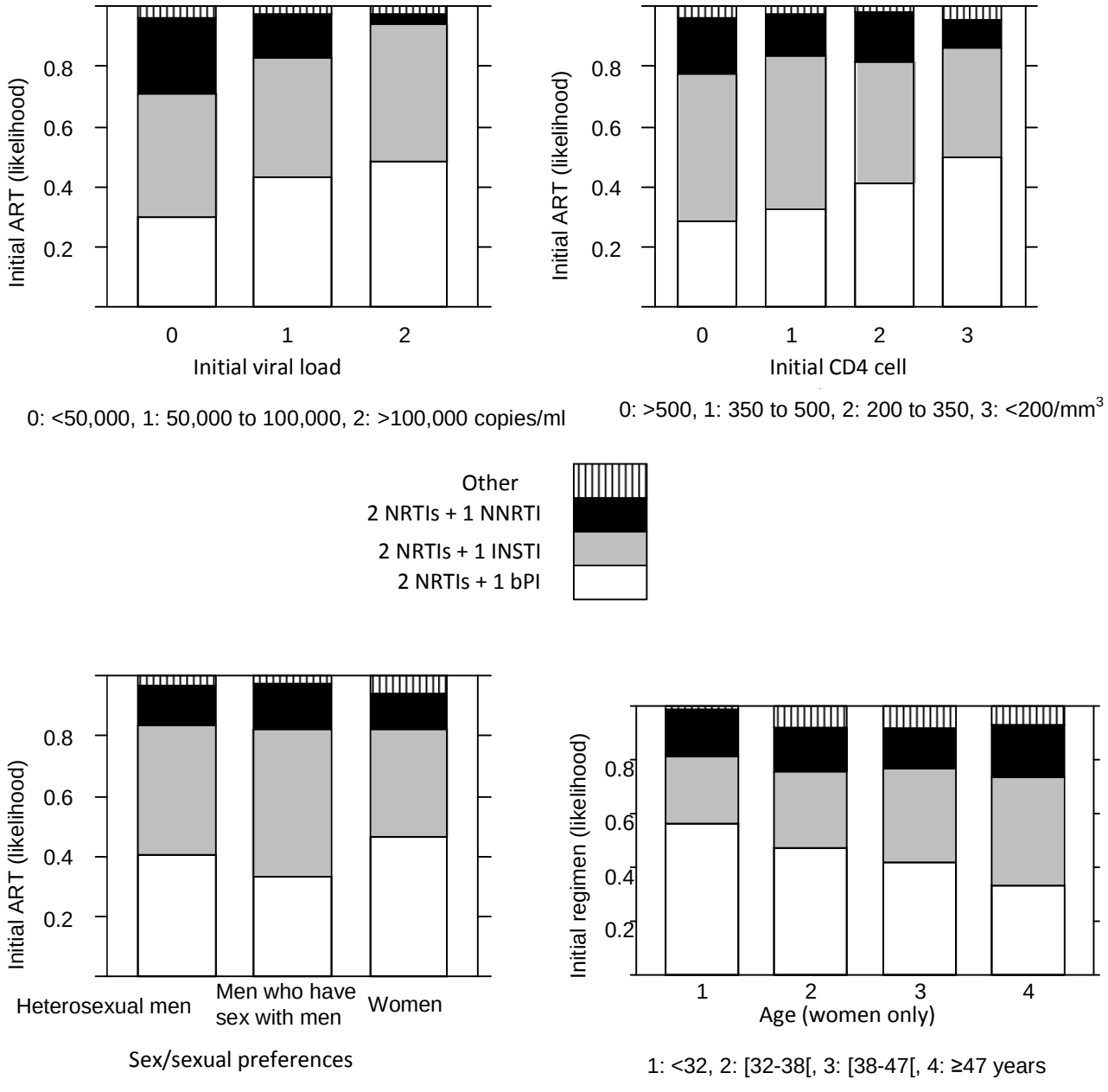

Tableau 1. Caractéristiques des patients et choix du traitement initial au cours des 10 dernières années

Table 1. Characteristics of patients and choice of first-line antiretroviral treatment over the past 10 years

		2005 N=1,156	2006 N=1,243	2007 N=1,254	2008 N=1,407	2009 N=1,432	2010 N=1,585	2011 N=1,625	2012 N=1,539	2013 N=1,624	2014 N=1,590	2015 N=1,442
Sex (% of men)		62.7	64.0	65.7	66.0	71.4	70.5	71.2	72.2	74.8	72.9	73.8
Men's age at ART initiation*		40 [34-47]	41 [34-48]	41 [34-48]	41 [34-48]	40 [34-48]	40 [33-48]	39 [32-47]	38 [31-47]	38 [30-47]	38 [29-47]	38 [30-48]
Women's age at ART initiation*		34 [28-42]	34 [28-42]	35 [29-42]	36 [30-44]	36 [29-43]	36 [29-45]	36 [29-47]	36 [30-47]	36 [29-46]	37 [31-47]	38 [32-47]
Initial viral load*, log_{10}copies/ml		4.8 [4.1-5.4]	4.8 [4.1-5.3]	4.7 [4.1-5.2]	4.7 [4.0-5.4]	4.7 [4.1-5.3]	4.8 [4.2-5.3]	4.7 [4.1-5.2]	4.8 [4.2-5.3]	4.7 [4.1-5.2]	4.5 [3.9-5.1]	4.6 [3.9-5.1]
Initial CD4 levels, cells/mm^{3*}		232 [121-334]	240 [133-334]	256 [139-341]	268 [167-358]	302 [182-407]	317 [199-418]	343 [209-453]	356 [220-485]	381 [226-532]	403 [230-580]	390 [206-562]
Acquisition mode (%)												
	MSM	30.3	34.7	36.9	38.1	43.2	42.4	45.6	47.1	48.8	47.2	46.1
	Heterosexual	54.2	51.9	49.4	48.9	45.6	46.1	42.8	42.6	40.2	42.5	42.3
	IVDU	4.8	4.6	4.7	3.9	3.1	2.7	2.8	2.3	1.8	1.3	2
	Other	10.6	8.8	8.9	9.1	8.1	8.8	8.8	7.9	9.0	9.0	9.6
HBV/HCV coinfection (%)		16.4	15.4	16.2	16.6	14.6	13.1	12.4	11.0	9.7	8.1	9.4
Initial ART	3 NRTIs	5.9	2.4	1.7	0.8	0.3	0.1	0.3	0.1	0	0	0
	2 NRTIs + 1 NNRTI	25.0	27.5	28.0	29.9	30.7	29.2	25.1	28.5	32.7	28.5	17.8
	2 NRTIs + 1 bPI	61.8	62.9	64.0	60.9	57.5	57.0	61.1	57.1	53.3	44.2	38.1
	2 NRTIs + 1 INSTI	0.1	0.1	0.4	1.8	4.7	6.9	4.6	4.8	6.4	21.3	39.4
	Other	7.2	7.1	5.9	6.6	6.8	6.8	8.9	9.5	7.6	6.0	4.7

*median, interquartile range; ART: antiretroviral treatment; MSM: men who have sex with men; IVDU: intravenous drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; bPI: boosted protease inhibitor; INSTI: integrase strand transfer inhibitors