Country of birth is associated with discrepancies in the prescription of two-drug regimens in successfully treated people living with HIV in France

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ABSTRACT

Objectives. We aimed to examine the association of the country of birth and the other patients' characteristics with the prescription of two-drug regimens (2DRs) in virally suppressed PLWH in France.

Design. Observational study conducted from the national Dat'AIDS prospectively collected database.

Methods. We included all adults who were actively in care on 31st December 2020 in 26 French centers, with an HIV plasma viral load (pVL) <50 copies/mL for at least 6 months while on ART. Patients with chronic hepatitis B were excluded because they are not eligible to 2DRs. Univariate and multivariate logistic regressions were built to analyze relationships between patients' characteristics and receiving a 2DR.

Results. We analyzed data from 28 395 PLWH: 41.7% men who have sex with men, 31.7% women and 26.5% heterosexual men; 35% born abroad. Median age was 53 years (IQR 44-60); ART duration 14 years (8-23); duration of virological suppression 87 months (42-142). 2DRs (mainly dolutegravir/rilpivirine, 53.8%, or dolutegravir/lamivudine, 41.7%) were prescribed in 16.3% of the patients and were less common in the "born abroad" group (18.9% versus 11.5%). The multivariate model showed that individuals born in France were more likely to receive a 2DR (aOR: 1.62 [1.50-1.74]), independently of other characteristics. Older PLWH and those with higher CD4 T-cell counts were also more likely to receive a 2DR.

Conclusion. Despite unrestricted access to ART in France, independently from HIV disease parameters, PLWH born abroad were less likely to receive 2DRs as a maintenance regimen than those born in France. Qualitative data are needed to better understand physicians' prescribing practices.

INTRODUCTION

Recent studies have reported disparities in antiretroviral therapy (ART) prescribing in the United States [1] and France [2,3] as a first line based on race, ethnicity and/or country of birth. Non-White and foreign-born people living with HIV (PLWH) were less likely to receive integrase stand transfer inhibitor (INSTI)-containing regimens, or to receive them in the earliest calendar periods, than White and native people living with HIV. Social inequalities, differential access to private insurance, or presumed poor adherence to ART may partly explain these disparities.

Following these studies, we wanted to investigate possible differences in ART prescriptions among successfully treated PLWH, according to country of birth. We considered two-drug regimens (2DRs) as a beneficial maintenance therapy innovation for PLWH with no hepatitis B virus (HBV) coinfection, since 2DRs have been included in all international guidelines for several years [4,5]. We aimed to determine whether country of birth was associated with the prescription of 2DRs among PLWH undergoing viral suppression in France, where health coverage is universal, independent of social and economic conditions. Indeed, in France, the cost of all antiretroviral treatments is covered at 100% by the national health insurance system, with no advance payment by the patient.

METHODS

Information was extracted from the Dat'AIDS cohort (Clinicaltrials.gov reference: NCT02898987), approved by the French National Committee on Informatics and Human Rights (CNIL number: 1357652) [6].

In this observational study, we selected adult patients actively in care on 31st December 2020 in 26 centers, with an HIV plasma viral load (pVL) <50 copies/mL for at least 6 months while

on ART. We collected sex, place of birth ("France" or "abroad"), age (on 31st December 2020), duration from HIV diagnosis and ART initiation, duration of virological suppression (pVL <50 copies/mL), ongoing ART, CD4+T cell count nadir, and last CD4+T cell count. Patients with chronic hepatitis B (based on positive AgHBs) were excluded because they are not eligible to 2DRs, which do not include tenofovir. All data were censored on 1st January 2021.

Univariate and multivariate logistic regressions with backward elimination following p-values were built to analyze relationships between patients' characteristics and receiving a 2DR. The multivariable models at first included all the characteristics related with a 2DR in univariate analysis with a p-value <0.10, and then was step by step reduced, successively excluding characteristics with p-values ≥0.05. Only variables with p-values <0.05 were kept in the final model. All statistics were done using R (R Foundation for Statistical Computing, 2020).

RESULTS

We included 28 395 PLWH, including 18 525 (65%) who were born in France, and 9 870 (35%) who were born abroad. In the whole population, 67.2% were men, the median age was 53 years (IQR 44-60), ART duration 14 years (8-23); duration of virological suppression 87 months (42-142). Patients who were born abroad were younger, more often women, had shorter HIV and ART histories, and shorter duration of virological suppression (Table 1). 2DRs (mainly dolutegravir/rilpivirine, 53.8%, or dolutegravir/lamivudine, 41.7%) were prescribed in 16.3% of the patients and were less common in the "born abroad" group (18.9% versus 11.5%). Conversely, boosted protease inhibitor (bPI)-based regimens were more common in patients born abroad (7.7% versus 2.7%).

The multivariate model showed that individuals born in France were more likely to receive a 2DR (aOR: 1.62 [1.50-1.74]), independently of other characteristics (Table 2). Older PLWH and

those with higher CD4 T-cell counts were also more likely to receive a 2DR. Regarding the association of country of birth with the prescription of a 2DR, similar results were found when the study population was restricted to men (aOR: 1.29 [1.17-1.43]) (Supplementary File). Similar results were also found when the study population was restricted to individuals born in Sub-Saharan Africa, who counted for 59.6% of the "born abroad" group (aOR: 1.87 [1.70-2.07]) (Supplementary File).

DISCUSSION

Our results demonstrated clear disparities in the choice of ART in successfully treated PLWH in France. Patients who were not born in France were less likely to receive 2DRs, despite good adherence to ART, as evidenced by sustained viral suppression, and despite similar reimbursement of all antiretroviral regimens. We chose to focus our analysis on 2DRs, assuming that this therapeutic strategy is a benefit innovative option for PLWH [7], but we could also have conducted this analysis on antiretroviral classes (e.g., prescription of boosted-PI- or INSTI-containing ART). Indeed, the distribution of these classes suggested important differences in maintenance ART prescriptions by place of birth, as highlighted in previous studies among treatment-naive PLHIV [1–3].

The most widely used and currently recommended 2DRs are based on dolutegravir [4,5], as illustrated in our study population, where more than 90% of patients were on dolutegravir/rilpivirine or dolutegravir/lamivudine. Women could have been less likely to receive dolutegravir-based 2DRs in recent periods, due to concerns about fetal side effects in pregnancy and/or weight gain. The 2018 international alert on the increased risk of neural tube closure in women exposed to dolutegravir in early pregnancy in Botswana [8] may have had a lasting effect on prescribing practices among women, although this increased risk has

145 now been downgraded [9]. Weight gain associated with INSTI use [10] has been reported to
146 be more frequent in women of African heritage, especially if they were already overweight
147 [11,12]. Consequence of these weight gains are still unclear, and physicians may act with
148 cautiousness in women, especially in the more recent calendar periods of prescription.
149 However, the analysis restricted to men showed persistent disparities in ART choice.
150 In addition, as our study spanned the time period of the COVID-19 crisis, it is possible that care
151 provision at the end of the study period differed following place of birth. Indeed, it has
152 previously been reported that PLWH born abroad experienced more disruptions in care during
153 the Covid-19 epidemic than PLWH born in France [13]. This could also (partly) explain
154 differences in prescriptions.
155 2DRs have been shown to be non-inferior to 3DRs in maintaining control of HIV replication
156 while avoiding toxicities and ART drug interactions when tenofovir disoproxil fumarate and
157 bPIs were discontinued [14–16]. Age was related with higher probability of switching to 2DRs,
158 which may be driven by co-morbidities and the wish to avoid drug-drug interactions with co-
159 medications [17].
160 The strength of the study is the large prospectively followed population, allowing us to
161 perform sensitivity analyses. Nevertheless, there are limitations. We were not able to take in
162 account the individuals' social situation, which is not collected in the cohort. However, the
163 social situation should not be related to ART availability nor to the choice of the drugs in a
164 country with unrestricted access to treatment. Finally, being "born abroad" included various
165 situations. In our population, 59% of PLWH not born in France were of African origin, the
166 others coming from various places around the world. Thus, our results may not apply to PLWH
167 originate from North hemisphere countries, but they were too few to be analyzed in a
168 separate way.

169 Overall, our study shows important differences in ART prescriptions according to place of
170 birth, which cannot be explained by clinical or biological conditions. The study was not
171 designed to explore the mechanisms explaining these discrepancies, which suggest health
172 inequalities. Differences in education, information on therapeutic advances, and access to
173 clinical trials between PLWH born in France and abroad may contribute to this observation
174 [18,19]. Additionally, we cannot exclude that false beliefs – implicit or not – about racial
175 differences, can lead to different therapeutic attitudes according to race, ethnicity or country
176 of birth [20]. Qualitative work is needed to investigate those mechanisms.

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ETHICS STATEMENT

Information was extracted from the Dat'AIDS cohort (Clinicaltrials.gov reference: NCT02898987), approved by the French National Committee on Informatics and Human Rights (CNIL number: 1357652).

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This study was done as routine work and was not funded.

CONTRIBUTORSHIP STATEMENT

RP designed the study and wrote the first draft; MH and LC designed and performed the analysis; LH, CD, CA, TH, PD, DR and AM were responsible for data quality in the centers and provided useful advice in the discussion. AM was responsible for English editing.

Table 1. Patients' characteristics, depending on the place of birth.

		Born in France N = 18 467	Born abroad N = 9 870	*P*
Age (years)		55 [47-61]	49 [41,58]	<0.0001
Age (%)	<45 years	3 709 (51.6)	3 473 (48.4)	<0.0001
	45-53 years	4 760 (63.4)	2 752 (36.6)	
	54-60 years	5 158 (73.8)	1 834 (26.2)	
	>60 years	4 898 (73.1)	1 811 (26.9)	
Gender and sexual orientation (%)	Women	3 900 (43.5)	5 065 (56.5)	<0.0001
	MSM[1]	10 042 (84.5)	1 847 (15.5)	
	MSW[2]	4 575 (60.9)	2 937 (39.1)	
Duration from HIV diagnosis (years)		20 [11-28]	15 [9-21]	<0.0001
CD4+T cells nadir (cell/mm^3)		229 [103-348]	212 [102-323]	<0.0001
CD4+T cells nadir (%)	<200	8 022 (63.7)	4 571 (36.3)	<0.0001
	201-350	5 954 (64.3)	3 311 (35.7)	
	351-500	2 855 (67.8)	1 356 (32.2)	
	>500	1 688 (72.9)	629 (27.1)	
Duration from first line of ART (years)		16 [9-24]	13 [7-19]	<0.0001
Duration of viral suppression (months)		122 [69-177]	90 [46-150]	<0.0001
Ongoing ART (%)	2 NRTIs[3]+ 1 bPI[4]	517 (39.9)	780 (60.1)	<0.0001
	2 NRTIs[3] + 1 NNRTI[5]	4 925 (63.4)	2 842 (36.6)	
	2 NRTIs[3] + 1 INSTI[6]	7 786 (63.8)	4 410 (38.2)	
	Two-drug regimen	3 499 (75.7)	1 125 (24.3)	
	Other	1 798 (71.6)	713 (28.4)	
Last CD4+T cells (cell/mm^3)		706 [525-927]	638 [472-841]	<0.0001
Last CD4+T cells (%)	<200	348 (61.3)	220 (38.7)	<0.0001
	200-350	1 188 (58.4)	846 (41.6)	
	350-500	2 475 (58.4)	1 764 (41.6)	
	>500	14 311 (67.2)	6 985 (32.8)	
Number of ART lines		5 [3-9]	5 [3-7]	<0.0001

NOTES. All variables were fully assessed except for gender: 7 missing values for patients born in France and 23 for patients born abroad and last CD4+T cells: 206 missing values for patients born in France and 55 for patients born abroad. 1. Men having sex with men. 2. Men having sex with women. 3. Nucleosidic reverse transcriptase inhibitor. 4. Boosted protease inhibitor. 5. Non-nucleosidic reverse transcriptase inhibitor. 6. Integrase strand transfer inhibitor.

Table 2. Patients' characteristics related with being treated by a 2-drug regimen.

		OR, 95%CI Univariate	aOR, 95%CI Multivariate
Age (years)	<44	Ref.	Ref.
	45-53	1.46 [1.33-1.61]	1.40 [1.27-1.55]
	53-60	1.80 [1.64-1.98]	1.66 [1.50-1.83]
	>61	2.39 [2.18-2.63]	2.25 [2.04-2.48]
Born in France		1.81 (1.68-1.94)	1.62 [1.50-1.74]
Gender and sexual orientation	Women	Ref.	-
	MSM[1]	1.29 [1.20-1.40]	-
	MWW[2]	1.07 [0.98-1.17]	-
Duration from HIV diagnosis (per year)		1.03 (1.02-1.03)	-
CD4+T cells nadir (cell/mm^3)	<200	Ref.	-
	200-350	1.00 [0.93-1.07]	-
	350-500	0.93 [0.85-1.03]	-
	>500	0.85 [0.75-0.96]	-
Duration from first line of ART (per year)		1.04 [1.03-1.04]	-
Duration of viral suppression (months)		1.00	-
Last CD4+T cells (cell/mm^3)	<200	Ref.	Ref.
	200-350	1.34 [1.00-1.80]	1.33 [0.99-1.79]
	350-500	1.40 [1.07-1.86]	1.44 [1.10-1.92]
	>500	1.62 [1.25-1.13]	1.68 [1.30-2.22]
Number of ART lines (for 1)		1.07 [1.07-1.08]	-

1. Men having sex with men. 2. Men having sex with women.

Supplementary Table 1. Patients' characteristics, depending on the place of birth (analysis restricted to men).

		Born in France N = 14 554	Born abroad N = 4 572	*P*
Age (years)		54 [47-61]	53 [43-61]	<0.0001
Age (%)	<45 years	3 592 (70.3)	1 521 (29.7)	<0.0001
	45-53 years	3 718 (78.2)	1 035 (21.8)	
	54-60 years	3 790 (79.2)	994 (20.8)	
	>60 years	3 454 (77.2)	1 022 (22.8)	
Gender and sexual orientation (%)	MSM[1]	9 979 (85.9)	1 635 (14.1)	<0.0001
	MSW[2]	4 575 (60.9)	2 937 (39.1)	
Duration from HIV diagnosis (years)		18 [10-27]	15 [8-23]	<0.0001
CD4+T cells nadir (cell/mm^3)		235 [106-357]	203 [85-323]	<0.0001
CD4+T cells nadir (%)	<200	6 130 (73.2)	2 244 (26.8)	<0.0001
	201-350	4 630 (76.6)	1 411 (23.4)	
	351-500	2 389 (79.2)	591 (19.8)	
	>500	1 405 (81.2)	326 (18.8)	
Duration from first line of ART (years)		15 [8-23]	12 [7-19]	<0.0001
Duration of viral suppression (months)		120 [69-175]	92 [48-153]	<0.0001
Ongoing ART (%)	2 NRTIs[3]+ 1 bPI[4]	354 (62.9)	209 (37.1)	<0.0001
	2 NRTIs[3] + 1 NNRTI[5]	3 891 (76.7)	1 186 (23.3)	
	2 NRTIs[3] + 1 INSTI[6]	6 302 (74)	2 218 (26)	
	Two-drug regimen	2 695 (81.8)	598 (18.2)	
	Other	1 312 (78.4)	361 (21.6)	
Last CD4+T cells (cell/mm^3)		693 [515-906]	614 [447-822]	<0.0001
Last CD4+T cells (%)	<200	273 (62.2)	133 (32.8)	<0.0001
	200-350	1 020 (67.9)	482 (32.1)	
	350-500	2 021 (69.6)	884 (30.4)	
	>500	11 100 (78.4)	3 050 (21.6)	
Number of ART lines		5 [3-9]	4 [3-7]	<0.0001

NOTES. 1. Men having sex with men. 2. Men having sex with women. 3. Nucleosidic reverse transcriptase inhibitor. 4. Boosted protease inhibitor. 5. Non-nucleosidic reverse transcriptase inhibitor. 6. Integrase strand transfer inhibitor.

Supplementary Table 2. Patients' characteristics related with being treated by a 2-drug regimen (analysis restricted to men).

		OR, 95%CI Univariate	aOR, 95%CI Multivariate
Age (years)	<44	Ref.	Ref.
	45-53	1.23 [1.09-1.37]	-
	53-60	1.38 [1.24-1.54]	-
	>61	1.94 [1.75-2.16]	-
Born in France		1.51 [1.37-1.66]	1.29 [1.17-1.43]
Gender and sexual orientation	MSM[1]	Ref.	Ref.
	MWW[2]	0.81 [0.75-0.88]	0.86 [0.79-0.94]
Duration from HIV diagnosis (per year)		1.02 [1.01-1.02]	-
CD4+T cells nadir (cell/mm^3)	<200	Ref.	-
	200-350	1.03 [0.94-1.12]	-
	350-500	0.99 [0.88-1.10]	-
	>500	0.82 [0.71-0.95]	-
Duration from first line of ART (per year)		1.03 [1.02-1.03]	-
Duration of viral suppression (months)		1.00 [1.00-1.00]	-
Last CD4+T cells (cell/mm^3)	<200	Ref.	Ref.
	200-350	1.53 [1.08-2.19]	1.60 [1.13-2.31]
	350-500	1.71 [1.24-2.41]	1.85 [1.33-2.64]
	>500	1.86 [1.37-2.61]	2.19 [1.59-3.08]
Number of ART lines (for 1)		1.07 [1.06-1.08]	1.06 [1.05-1.07]

NOTES. 1. Men having sex with men. 2. Men having sex with women.

Supplementary Table 3. Patients' characteristics, depending on the place of birth (analysis restricted to PLWH originated from Sub-Saharan Africa).

		Born in France N = 18 456	Born abroad N = 5 887	*P*
Age (years)		55 [47-61]	47 [40-55]	<0.001
Age (%)	<45 years	3 951 (60.4)	2 594 (39.6)	<0.0001
	45-53 years	4 403 (73.4)	1 593 (26.6)	
	54-60 years	5 178 (84.8)	926 (15.2)	
	>60 years	4 924 (87.1)	731 (12.9)	
Gender and sexual orientation (%)	Women	9 985 (97.5)	260 (2.5)	<0.0001
	MSM[1]	4 576 (73.5)	1 646 (26.5)	
	MSW[2]	3 888 (49.7)	3 937 (50.3)	
Duration from HIV diagnosis (years)		20 [11-28]	15 [8-19]	<0.001
CD4+T cells nadir (cell/mm^3)		231 [105-351]	218 [114-324]	<0.001
CD4+T cells nadir (%)	<200	7 908 (75.2)	2 613 (24.8)	<0.0001
	201-350	5 917 (74.4)	2 039 (25.6)	
	351-500	2 868 (77)	853 (23)	
	>500	1 763 (83.9)	339 (16.1)	
Duration from first line of ART (years)		16 [9-24]	12 [7-17]	<0.001
Duration of viral suppression (months)		97 [50-151]	64 [31-114]	<0.001
Ongoing ART (%)	2 NRTIs[3]+ 1 bPI[4]	493 (45.8)	583 (54.2)	<0.0001
	2 NRTIs[3] + 1 NNRTI[5]	4 940 (73)	1 824 (27)	
	2 NRTIs[3] + 1 INSTI[6]	7 767 (75.6)	2 5608 (24.4)	
	Two-drug regimen	3 492 (86.4)	548 (13.6)	
	Other	1 764 (82.2)	381 (17.8)	
Last CD4+T cells (cell/mm^3)		707 [527-928]	617 [461–803]	<0.001
Last CD4+T cells (%)	<200	332 (73.9)	117 (26.1)	<0.001
	200-350	1 163 (69)	523 (31)	
	350-500	2 470 (68.1)	1 161 (31.9)	
	>500	14 286 (78.1)	4 013 (21.9)	
Number of ART lines		5 [3-9]	4 [3-7]	<0.001

NOTES. 1. Men having sex with men. 2. Men having sex with women. 3. Nucleosidic reverse transcriptase inhibitor. 4. Boosted protease inhibitor. 5. Non-nucleosidic reverse transcriptase inhibitor. 6. Integrase strand transfer inhibitor.

Supplementary Table 4. Patients' characteristics related with being treated by a 2-drug regimen (analysis restricted to PLWH originated from Sub-Saharan Africa).

		OR, 95%CI Univariate	aOR, 95%CI Multivariate
Age (years)	<44	Ref.	Ref.
	45-53	1.48 [1.33_1.64]	1.22 [1.09-1.35]
	53-60	1.78 [1.61-1.96]	1.24 [1.11-1.38]
	>61	2.34 [2.12-2.58]	1.60 [1.44-1.78]
Born in France		2.25 [2.05-2.48]	1.87 [1.70-2.07]
Gender and sexual orientation	Women	Ref.	Ref.
	MSM[1]	1.36 [1.26-1.48]	-
	MWW[2]	1.09 [0.99-1.19]	-
Duration from HIV diagnosis (per year)		1.03 [1.02-1.03]	-
CD4+T cells nadir (cell/mm^3)	<200	Ref.	-
	200-350	0.99 [0.91-1.07]	-
	350-500	0.90 [0.81-0.99]	-
	>500	0.86 [0.75-0.98]	-
Duration from first line of ART (per year)		1.04 [1.03-1.04]	-
Duration of viral suppression (months)		1.00 [1.00-1.00]	-
Last CD4+T cells (cell/mm^3)	<200	Ref.	-
	200-350	1.10 [0.82-1.51]	-
	350-500	1.16 [0.88-1.56]	-
	>500	1.33 [1.02-1.77]	-
Number of ART lines (for 1)		1.07 [1.06-1.08]	1.06 [1.05-1.07]

NOTES. 1. Men having sex with men. 2. Men having sex with women.