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Doravirine plus lamivudine two-drug regimen as maintenance antiretroviral therapy in people living with HIV: a French observational study

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1 **Title**

2 **Doravirine plus lamivudine (DOR+3TC) two-drug regimen as a maintenance antiretroviral**
3 **therapy in people living with HIV: a French observational study**

4

5 **Running title**

6 Doravirine plus lamivudine as a maintenance ART

7

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35 **ABSTRACT**

36 **Background.** Two-drug regimens based on integrase strand transfer inhibitors (INSTIs) and
37 boosted PIs has entered recommended ART. However, INSTIs and boosted PIs may not be
38 suitable for all patients. We aimed to report our experience with doravirine/lamivudine
39 (DOR+3TC) as maintenance therapy in PLWH followed in French HIV settings.

40 **Methods.** This observational study enrolled all adults who initiated DOR+3TC between
41 09/01/2019 and 10/31/2021, in French HIV centers participating in the Dat'AIDS cohort. The
42 primary outcome was the rate of virological success (plasma HIV-RNA <50 copies/mL) at W48.
43 Secondary outcomes included: rate of treatment discontinuation for non-virological reasons,
44 evolution of CD4 count and CD4/CD8 ratio over follow-up.

45 **Results.** Fifty patients were included, with 34 (68%) men, median age: 58 years (IQR 51-62),
46 ART duration: 20 years (13-23), duration of virological suppression: 14 years (8-19), CD4 count:
47 784/mm³ (636-889). Prior switching, all had plasma HIV-RNA <50 copies/mL. All but three
48 were naive to doravirine, and 36 (72%) came from a three-drug regimen. Median follow-up
49 was 79 weeks (IQR 60-96). Virological success rate at W48 was 98.0% (95%CI 89.4-99.9). One
50 VF occurred at W18 (HIV-RNA=101 copies/mL) in a patient who briefly discontinued DOR+3TC
51 due to intense nightmares; no resistance at baseline; no resistance emergence. There were
52 three strategy discontinuations for adverse event (digestive disorders: n=2, insomnia: n=1).
53 There was no significant change in CD4/CD8 ratio, while CD4 T-cell count significantly
54 increased.

55 **Conclusion.** These preliminary findings suggest that DOR+3TC regimen can maintain high
56 levels of viral suppression in highly ART-experienced PLWH with long-term viral suppression,
57 and good CD4+T cells count.

58 INTRODUCTION

59 Although current antiretroviral treatments have improved in terms of efficacy, robustness,
60 genetic barrier to resistance and tolerability, people living with HIV (PLWH) remain exposed
61 to drug toxicity for several decades. Two-drug regimens (2DRs) are now recommended in
62 international guidelines as maintenance regimens for virally suppressed PLWH to limit long-
63 term cumulated toxicity of certain drugs.^{1,2} Recommended 2DRs include oral boosted-
64 PI/lamivudine (bPI/3TC), dolutegravir/lamivudine (DTG/3TC) and dolutegravir/rilpivirine
65 (DTG/RPV), and injectable cabotegravir+rilpivirine (CAB+RPV). However, not all PLWH are able
66 to receive integrase strand transfer inhibitor- (INSTI-) or bPI-based 2DRs, in the event of past
67 intolerance, resistance or drug-drug interaction.

68 2DRs not based on INSTIs or bPIs could be a suitable treatment option in these patients, but
69 data to support this are almost non-existent. Until now, only one, small pilot study has
70 evaluated the virological efficacy of a 2DR based on an NNRTI plus an NRTI. In 2020, Kahlert,
71 *et al.* demonstrated that nevirapine/lamivudine (NVP/3TC) was able to maintain control of
72 viral replication (plasma HIV-RNA <50 copies/mL) in 19 patients over 144 weeks.³

73 Doravirine is a new generation NNRTI with very few drug interactions and a better genetic
74 barrier than older NNRTIs. It has been approved in Europe for treatment-naïve and treatment-
75 experienced PLWH, following large trials that demonstrated its virological efficacy and good
76 safety profile.⁴⁻⁶ Its combination with lamivudine, as a 2DR, has never been investigated.

77 Although not a recommended strategy, some patients have received DOR+3TC because of
78 their virological and therapeutic history. Herein, we aimed to report the reasons for switching,
79 as well as the ability of DOR+3TC to maintain virological control in PLWH followed in five
80 French centers.

81

82 **METHODS**

83 Information was collected from centers participating in the French Dat'AIDS cohort
84 (Clinicaltrials.gov reference: NCT02898987) after approval by the Nantes Institutional Review
85 Board and the French National Committee on Informatics and Human Rights (CNIL number:
86 1357652). The Dat'AIDS cohort is an ongoing cohort, started in 2000, including at that time all
87 PLWH with their previous medical history, and all new PLWH in care since then have become
88 part of the cohort, after they were fully informed and provided written consent.⁷

89 This observational, non-interventional study included all adults who switched to DOR+3TC
90 between 09/01/2019 and 01/31/2022, with at least 24 weeks of follow-up at time of analysis,
91 in 5 HIV centers (i.e., centers with at least one patient meeting the inclusion criteria): Quimper,
92 Pitié-Salpêtrière (Paris), Rennes, Pointe-à-Pitre and Marseille. ART prescriptions were made
93 during routine follow-up by HIV physicians, and were not part of any protocol. However, all
94 these prescriptions were discussed in local ART committees, independently of this analysis.
95 There were no additional biological sample or questionnaire used for this study. Past HIV-RNA
96 and HIV-DNA resistance genotypes were collected, and the cumulative genotype combined all
97 past genotypic tests with an updated interpretation using the latest version of the ANRS
98 algorithm (www.hivfrenchresistance.org). We also collected the reasons associated with the
99 switch to DOR+3TC.

100 The primary outcome was maintenance of virological suppression (HIV-RNA <50 copies/mL)
101 at W48. Virological failure [VF] was defined as a confirmed HIV-RNA ≥50 copies/mL, or a single
102 HIV-RNA ≥200 copies/mL, or ≥50 copies/mL with ART change. Secondary outcomes included:
103 strategy success rate (no VF and no ART change for non-virological reasons), number of ART
104 discontinuations, emergence of genotypic resistance in the event of VF, evolution of CD4 T-
105 cell counts and CD4/CD8 ratio over follow-up.

106 Changes in body weight, CD4 T-cell counts and CD4/CD8 ratio were assessed using the
107 Wilcoxon test. Statistical tests were processed using STATA v.14.

108

109 **RESULTS**

110 Fifty patients switched for DOR+3TC, including 41 who reached 48 weeks of follow-up. Median
111 follow-up was 79 weeks (IQR 60-96). Patients' characteristics are detailed in Table 1. Thirty-
112 four of them (68%) were men. Median age was: 58 years (IQR 51-62), ART duration: 20 years
113 (IQR 13-23), duration of virological suppression: 14 years (IQR 8-19), CD4 T-cell count:
114 784/mm³ (IQR 636-889). All had plasma HIV-RNA <50 copies/mL at study entry. Prior to
115 switching, all except three were naive to doravirine, and 36 (72%) were receiving a three-drug
116 regimen (3DR). Genotypic data (past RNA and DNA resistance genotypes) were available for
117 20 patients, with no resistance to both doravirine and lamivudine in 18 patients, and a past
118 M184V mutation in 2 patients, conferring resistance to lamivudine. The M184V mutations
119 were found on an RNA resistance genotype performed 9 and 11 years prior to switch, in two
120 patients with prolonged durations of viral suppression before switching (8 and 11 years,
121 respectively).

122 The main reason for physicians to switch ART to DOR+3TC was to reduce the drug burden, and
123 to prevent long-term toxicities and drug interactions, in 32 patients with long term viral
124 suppression (>10-15 years) on stable 3DR. Six patients had adverse events to ongoing ART,
125 motivating an immediate switch to DOR+3TC: osteoporotic bone fracture on tenofovir
126 disoproxil fumarate (TDF) (n=2), fast weight gain on INSTI (n=2), digestive discomfort on
127 rilpivirine (n=1), and myalgia with increased CPK levels on bictegavir (n=1). Twelve presented
128 a significant drug interaction, motivating an immediate switch to DOR+3TC: rilpivirine and
129 proton pump inhibitor (n=7), and bPI and comedications (n=5). In addition to those reasons,

130 the use of certain antiretroviral classes needed to be avoided, due to past side effects,
131 restricting treatment options: weight gain under INSTI with or without tenofovir alafenamide
132 (TAF) (n=10), weight gain under TAF with no associated INSTI (n=1), neuropsychic intolerance
133 under INSTI (n=7), marked lipodystrophy attributable to past NRTIs (n=3).

134 One VF occurred at W18 (plasma HIV-RNA=101 copies/mL), leading to a virological success
135 rate of 98.0% (95%CI 89.4-99.9) at W48 (Figure 1a). This VF occurred in a patient who briefly
136 stopped his treatment due to intense nightmares. There was no resistance at baseline, and no
137 resistance emerged had time of VF (HIV-RNA successfully amplified). The patient achieved a
138 plasma HIV-RNA <50 copies/mL after resumption of boosted PI monotherapy. There were
139 three other strategy discontinuations over the entire study period for adverse event (digestive
140 disorder: n=2, insomnia: n=1), leading to a strategy success rate of 92.0% (95%CI 80.8-97.8) at
141 W48 (Figure 1b).

142 There was no significant change in the body weight (-0.1 kg, p=0.83), the CD4/CD8 ratio (+0.01,
143 p=72), and we observed a significant increase in the CD4 T-cell counts (+51/mm³, p=0.031)
144 over the study period.

145

146 **DISCUSSION**

147 We reported a series of 50 PLWH with a long duration of viral suppression, who were switched
148 by their HIV physician to DOR+3TC, with high level of virological success (98%) at W48. Only
149 one VF occurred, in a patient who briefly discontinued DOR+3TC, as attested by low-level of
150 plasma HIV-RNA. Importantly, there was no emergence of resistance at time of virological
151 rebound. All other PLWH remained virally controlled. There was no decrease in CD4 T-cell
152 counts or CD4/CD8 ratio on DOR+3TC, as previously shown in larger studies evaluating other
153 2DRs as maintenance regimens.⁸⁻¹¹ The DOR+3TC combination was well tolerated, particularly

154 with regard to weight, with no significant variation over the study period.

155 All prescriptions were made in real-life conditions, outside of any protocolized trial. This
156 explains why the characteristics of the patients are fairly different from those of the
157 participants usually included in clinical trials. Although they had high current CD4 T-cell counts
158 ($>700/\text{mm}^3$), associated with a long duration of viral suppression (14 years), 22% of them had
159 an AIDS-related event in their history. We assume that a significant number of them received
160 toxic and ineffective antiretroviral combinations at the start of treatment. The main reasons
161 for choosing DOR+3TC mentioned by clinicians were past or present side effects and drug
162 interactions. These are indeed two major concerns in the daily practice of managing aging
163 PLWH.

164 Two-drug suppressive therapies are increasingly important in a context of lifelong required
165 ART.¹² The benefit of 2DRs, such as DTG/3TC, DTG/RPV or etravirine/raltegravir (ETR/RAL), has
166 been demonstrated through improved metabolic, renal and bone biomarkers.^{8,9,13} Prevention
167 of cardiovascular and renal function impairment, as well as bone fracture risk attributable to
168 ART, is a key concern for PLWH who are all aging. In addition, these strategies avoid most of
169 the drug interactions. However, all PLWH are not able to receive INSTI-based 2DRs, as
170 evidenced in the sample of patients presented here, e.g., in cases of neuropsychological
171 intolerance or weight gain from previous INSTI exposure. Previous studies have shown the
172 robustness and the good tolerance of doravirine, which did not appear to cause excessive
173 weight gain, unlike INSTIs and TAF. Real-life data are starting to confirm that doravirine-based
174 combinations are safe in terms of metabolic and weight issues.^{14,15} Finally, the cost of the
175 DOR+3TC combination, which does not exist as a fixed-dose, is lower than for other usual
176 2DRs.

177 Our study has some limitations, as it is a retrospective observational study including a limited

178 number of patients. The lack of a comparative arm clearly limits the significance of this
179 analysis. Many resistance genotypes were missing, as is often the case for patients with a long
180 history of HIV infection. However, our preliminary findings suggest that DOR+3TC regimen is
181 able to maintain high levels of viral suppression in selected highly ART-experienced PLWH with
182 long-term viral suppression, and restored CD4+T cells count. Given the interesting virological
183 and pharmacological profile of both doravirine and lamivudine, we argue for a larger
184 comparative maintenance trial evaluating the efficacy of the DOR+3TC combination.

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247

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304

305 **Table 1. Patients' characteristics at baseline (N=50).**

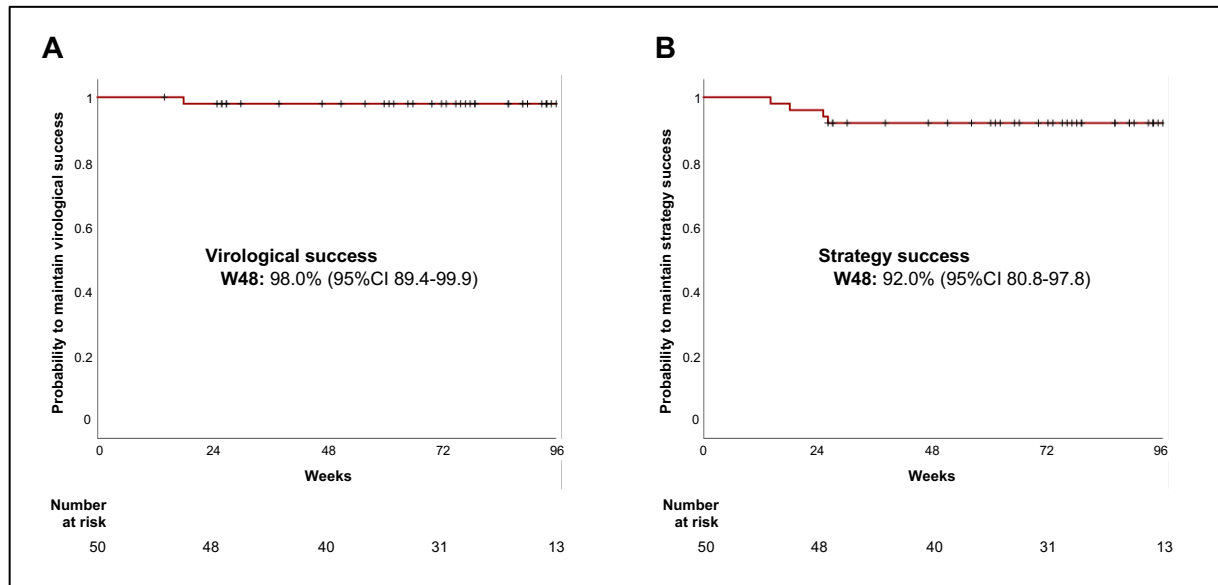
Age, years, median (IQR)	58 (51-62)
Gender, n (%)	
- Male	34 (68)
- Female	16 (32)
Birth Country, n (%)	
- France	44 (88)
- Other	6 (12)
Transmission group, n (%)	
- Heterosexual	23 (46)
- MSM	21 (42)
- Other	6 (12)
Comorbidities, n (%)	
- Treated diabetes	6 (12)
- Treated high blood pressure	17 (34)
- Dyslipidemia	22 (44)
- Kidney disease	5 (10)
- Osteoporosis	7 (14)
Body weight, kg, median (IQR)	73.9 (66.3-85.0)
CDC stage C, n (%)	11 (22)
CD4 T-cell nadir, cells/mm³, median (IQR)	258 (145-385)
HIV-RNA zenith, log₁₀ copies/mL, median (IQR)	4.79 (3.67-5.32)
Time from HIV diagnosis, years, median (IQR)	24 (16-29)
Time from ART initiation, years, median (IQR)	20 (13-23)
Previous virological failure on NNRTI, n (%)	0 (0)
Previous virological failure on 3TC or FTC, n (%)	3 (6)
Genotypic sensitivity score to DOR+3TC^a, n (%)	
- 1	2 ^b /20 (10)
- 2	18/20 (90)
Duration of viral suppression, years, median (IQR)	14 (8-19)
CD4 T-cell count, cells/mm³, median (IQR)	784 (636-889)
CD4/CD8 ratio, median (IQR)	1.16 (0.96-1.50)
Antiretroviral strategy prior to DOR+3TC, n (%)	
- NNRTI-based 3DR	24 (48)
- INSTI-based 3DR ^c	12 (24)
- Dolutegravir/lamivudine	6 (12)
- Darunavir/ritonavir/lamivudine	3 (6)
- Other 2DR	3 (6)
- Boosted PI monotherapy	2 (4)

306

307 NOTES. 3DR: three-drug regimen. 2DR: two-drug regimen. a. Calculated from cumulative
 308 historical HIV-RNA and HIV-DNA genotypes with reverse transcriptase available sequences
 309 (N=20). b. These two patients had a documented M184V mutation in past RNA genotypes, in

310 2010 and 2011. c. These NNRTI-based 3DR included rilpivirine (n=11), nevirapine (n=9),
311 doravirine (n=3) and efavirenz (n=1).

312 Figure 1. Virological success rate (A), and strategy success rate (B) under DOR+3TC over time.



313