

## **Impact of obesity on antiretroviral pharmacokinetics and immuno-virological response in HIV-infected patients: a case-control study**

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1 **TITLE PAGE:**

2 **Title: Impact of obesity on antiretroviral pharmacokinetics and immuno-virological**  
3 **response in HIV-infected patients: a case-control study**

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23 **ABSTRACT:**

24 **Background:** Obesity has a large prevalence among HIV-infected patients. Increased adipose  
25 tissue mass affects the pharmacokinetics of numerous drugs, but only a few data are available  
26 for antiretroviral drugs.

27 **Objective:** In this study, we aimed to explore the pharmacokinetics of antiretroviral drugs and  
28 the immune-virological response in obese patients with HIV infection.

29 **Patients and methods:** We examined data from 2009 to 2012 in our hospital's database for  
30 HIV-1-infected patients who received an antiretroviral drug among abacavir, emtricitabine,  
31 lamivudine, tenofovir, efavirenz, etravirine, nevirapine, atazanavir/ritonavir,  
32 darunavir/ritonavir, lopinavir/ritonavir and raltegravir. Obese patients were defined with body  
33 mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> and normal-weight patients with BMI 19–25 kg/m<sup>2</sup>. Plasma  
34 concentrations (C<sub>12/24h</sub>) were compared for each antiretroviral using Mann-Whitney test.  
35 Suboptimal dosing and virological outcome were assessed by logistic regression, adjusting on  
36 covariates.

37 **Results:** We enrolled 291 obese and 196 normal-weight patients. Among the 12 analyzed  
38 antiretroviral drugs, tenofovir, efavirenz and lopinavir C<sub>12h</sub> were significantly lower in obese  
39 than normal-weight patients: 66 versus 86 ng/mL, 1,498 versus 2,034 ng/mL and 4,595 versus  
40 6,420 ng/mL respectively ( $P < 0.001$ ). Antiretroviral C<sub>12/24h</sub> were more frequently below  
41 efficacy thresholds for obese than normal-weight patients after adjustment for other covariates  
42 ( $P < 0.001$ ). Although obese patients showed higher CD4 count than normal-weight (510 vs  
43 444 cells/ $\mu$ L,  $P < 0.001$ ), the groups did not differ in virological failure rate.

44 **Conclusion:** This study highlights the impact of obesity on antiretroviral plasma exposure, but  
45 identifies no consequence of this suboptimal exposure on the immuno-virological control in  
46 this population.

## 47 **Introduction**

48 Obesity has reached a high prevalence among patients living with HIV infection during the last  
49 2 decades.<sup>1,2</sup> Several reasons might explain this evolution. First, available highly active  
50 antiretroviral (ARV) treatments have led to increased virological control in about 88% of  
51 treated patients in France,<sup>3</sup> thereby leading to global aging of the HIV-infected population.<sup>4</sup>  
52 Second, the increasing number of patients with access to ARV, and the recent change of  
53 American and European recommendations to treat most of patients from the diagnostic of  
54 infection would impact prevalence, as ARV initiation was demonstrated to be strongly  
55 associated to weight gain and obesity.<sup>2</sup> Third, the increase in obesity is a worldwide  
56 multifactorial trend, due to increased calories intake and lifestyle evolution.<sup>5</sup>

57 Besides its association with cardiovascular events, obesity may affect medical care, in particular  
58 the dosing and pharmacokinetics of administered drugs. Obese people present varied body  
59 composition and regional blood circulation as compared with non-obese people<sup>6</sup> affecting the  
60 body disposition of numerous therapeutic agents and therefore plasma concentrations, related  
61 in most cases to the drug activity.<sup>7,8</sup> Thus, obesity may be a concern for treatment with several  
62 ARV agents. In particular, non-nucleoside reverse-transcriptase inhibitors (NNRTI), protease  
63 inhibitors (PI), and integrase inhibitors are lipophilic drugs and are susceptible to diffusion and  
64 entrapment in adipose tissue; their antiviral activity is related to drug plasma concentration.<sup>9</sup>  
65 Yet available data in this obese population are scarce. One study reported a decrease in  
66 efavirenz concentration in plasma and a large accumulation in adipocytes.<sup>10</sup> Therefore,  
67 assessing antiretroviral exposure in these patients can provide critical insight into their medical  
68 care and follow-up.

69 Obese patients living with HIV, in addition, show a specific response to the infection. Several  
70 studies have reported that non-treated obese or overweight patients show better immunological

71 control than normal-weight patients, with CD4+ T-cell count remaining higher despite similar  
72 control of plasma viral load,<sup>1,11</sup> and show lower risk of evolution to AIDS.<sup>12,13</sup> This superior  
73 immunological control was also found in obese patients receiving treatment, with faster  
74 recovery of CD4+ T-cell count after ARV initiation than in normal-weight patients.<sup>14,15</sup> Yet,  
75 the physiological features of this protection conferred by obesity are not well understood.  
76 Adipose tissue is not a favored site of HIV replication, with little recovery of viral RNA and  
77 integrated DNA,<sup>10</sup> although a recent study demonstrated potential implications for the tissue as  
78 a viral reservoir in HIV latency.<sup>16</sup> However, fat tissue widely contributes to an inflammatory  
79 state, with a notably large release of cytokines.<sup>17,18</sup> If this continuous inflammation may play a  
80 role in immunological control, it can lead to atherosclerosis and an increase in cardiovascular  
81 events.<sup>19</sup>

82 In this study, we evaluated the impact of obesity in HIV-infected patients on ARV plasma  
83 exposure and immuno-virological response. Viral load and ARV concentrations in plasma were  
84 assayed in a cohort of HIV-infected obese patients and normal-weight patients. We assessed  
85 the impact of obesity on plasma drug concentration for ARV of different classes, and the  
86 association of obesity with ARV efficacious plasma concentration and virological failure,  
87 adjusting for covariates.

## 88 **Patients and methods**

### 89 *Patients*

90 Source population was HIV-1-infected patients followed from January 2009 to December 2012  
91 in the university hospital Bichat-Claude Bernard, Paris for whom data were collected and  
92 available in the hospital electronic database. Patients were followed according to the French  
93 recommendations,<sup>3,20</sup> with viral load measurement and CD4+ T-cells count frequencies  
94 between 3 and 6 months. Therapeutic drug monitoring was commonly performed 15 to 30 days

95 after introduction of new drug for various indications, as potential drug-drug interactions,  
96 adverse event, virological failure, abnormal BMI or malabsorption suspicion.

97 Eligible patients were > 18 years old with available data on demographic characteristics, plasma  
98 viral load, CD4+ T-cell count and ARV plasma concentration. They had received at least one  
99 of the 11 ARV drugs abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate,  
100 efavirenz, nevirapine, etravirine, lopinavir, atazanavir, darunavir and raltegravir, the PIs being  
101 combined with ritonavir. We included obese patients with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>  
102 according to the WHO definition<sup>5</sup> who matched study eligibility criteria (Figure 1). Normal-  
103 weight patients were defined with BMI 19 to 25 kg/m<sup>2</sup>. Each was selected to correspond on age  
104 (+/- 5 years), gender, ethnicity (African, Caucasian, Hispanic, other origins), and ARV-based  
105 regimen to one patient of the obese group. Pregnant women after the fourth month of pregnancy,  
106 hepatitis C virus co-infected patients, and those with BMI 26 to 30 kg/m<sup>2</sup> were excluded. Data  
107 on demographics (age, gender, native country), infection (date of diagnosis, viral load, CD4+  
108 T-cell count) and ARV treatment (drug, dosing regimen, treatment initiation, date of current  
109 treatment initiation, characteristics at the date of ARV concentration sampling) were extracted  
110 from the HIV medical database.

111 Included patients were followed up to December 2015. Plasma HIV-RNA and BMI data were  
112 available for at least 1 year after ARV plasma concentration determination for all included  
113 patients. Then, the date of drug switch, defined by the addition or removal of at least one  
114 molecule, was recorded, as was viral load, BMI at this date, new treatment initiated, and the  
115 reason for treatment modification advocated by the physician.

## 116 ***Ethics***

117 All patients enrolled in this study gave their written informed consent to have their medical  
118 chart recorded in the electronic medical record system NADIS (Fedialis Medica, Marly Le Roi,

119 France, French National Commission on Informatics and Rights CNIL approval no. 1171457  
120 May 24, 2006, <http://www.nadis.fr/>), designed for the medical follow-up of HIV-infected  
121 patients, which also included their agreement to participate in retrospective studies.

### 122 ***ARV plasma concentration determination***

123 Blood samples were collected in the patients,  $12 \pm 2$  or  $24 \pm 4$  hr after the last ARV  
124 administration according to a twice-daily or once-daily ARV regimen, respectively, to assess  
125 minimal plasma concentrations (C12h or C24h), excepted for nucleoside reverse transcriptase  
126 inhibitors (NRTI) and efavirenz, for which C12h were considered. For this last molecule usually  
127 taken once daily on the evening, its long elimination half-life (44-55 h) leads to minor plasma  
128 concentration variation over day at steady state. On the contrary, abacavir and lamivudine short  
129 half-lives lead to high proportion of trough concentrations below the limit of quantification  
130 (LOQ), and most of the patients have available concentration 12 hours after the last intake.  
131 Only one sample was considered for each patient to maintain equal contribution of all the  
132 included patients in the analysis. ARV plasma concentrations were determined by liquid  
133 chromatography with tandem mass spectrometry (Acquity UPLC/TQD, Waters Corp., Milford,  
134 MA, USA) as described.<sup>21</sup> The LOQ was defined as 30 ng/mL for ritonavir; 20 ng/mL for  
135 efavirenz, nevirapine and lopinavir; and 5 ng/mL for atazanavir, darunavir, etravirine and  
136 raltegravir. Concentrations below the LOQ were set by convention as LOQ/2 for statistical  
137 analysis.

138 ARV plasma concentrations were interpreted with the thresholds of antiviral efficacy routinely  
139 used in patient follow-up in Bichat hospital, from the US National Institutes of Health  
140 recommendations<sup>9</sup> for atazanavir, efavirenz and nevirapine (150; 1,000 and 3,000 ng/mL,  
141 respectively) or from clinical study<sup>22-25</sup>, based on *in vitro* antiviral activity, for lopinavir,  
142 darunavir, etravirine and raltegravir (3,000; 550; 200 and 50 ng/mL, respectively). NRTI

143 C12/24h were interpreted regarding usual values corresponding to the respective daily doses.  
144 Tolerance thresholds were considered for atazanavir (850 ng/ml), lopinavir (8,000 ng/mL),  
145 efavirenz (4,000 ng/mL), etravirine (950 ng/mL) and nevirapine (6,000 ng/mL), for which a  
146 concentration–toxicity relationship was documented.<sup>3</sup> For tenofovir C12h, a toxicity threshold  
147 was previously determined at 160 ng/mL.<sup>26</sup>

148 No direct assessment of patient adherence to ARV treatment was available in the database,  
149 therefore indirect measure of patient adherence was estimated with the number of ARV  
150 concentrations below LOQ in each group.

### 151 *Immuno-virological assessment*

152 Plasma HIV-1 RNA was assessed by using the COBAS® AmpliPrep/COBAS® TaqMan®  
153 HIV-1 Test, v2.0 (Roche Molecular Systems, Branchburg, NJ), with an LOQ of 20 copies/mL.  
154 Virological failure was considered with least 2 consecutive plasma HIV-RNA > 50 copies/mL  
155 and otherwise virological success. Blood CD4+ T cells were counted by use of the FACSCanto  
156 II system (BD biosciences).

### 157 *Statistical analysis*

158 Data are reported as median and interquartile range (IQR: 25-75%). Demographic and infection  
159 characteristics were compared between obese and control group using Fisher exact test for  
160 categorical variable and non-parametric Mann-Whitney test for continuous variables. Plasma  
161 concentrations for each ARV drug were compared by Mann-Whitney test. Proportions of  
162 patients with concentrations below the efficacy threshold or above the toxicity threshold were  
163 compared for each drug, except ritonavir, abacavir, lamivudine and emtricitabine, by Fisher  
164 exact test. Multivariate logistic regression analysis was performed to explore the association of  
165 suboptimal dosing (defined as at least one ARV plasma concentration below the efficacy  
166 threshold) and virological failure with obesity, on the day of concentration assessment and at



167 one year of follow-up, adjusting on demographic and infection characteristics. Because of the  
168 few control patients included, matching was not considered for statistical analysis. Statistical  
169 analysis was performed using R software v3.2.2. (<https://cran.r-project.org/>).

## 170 **Results**

### 171 *Patients*

172 We identified 540 HIV-1 infected obese patients among the 4,500 usually followed at Bichat-  
173 Claude Bernard Hospital; 291 of them matched the study eligibility criteria and were included  
174 (Figure 1, Table 1). We included 196 normal-weight matched patients. We were unable to  
175 include controls for each selected obese patient because of the demographic characteristics of  
176 patients followed at Bichat-Claude Bernard hospital and in particular the large prevalence of  
177 obesity in African women, added to the fact that concentration assays were not systematic for  
178 normal weight patients, according to the French recommendations.<sup>20</sup> For obese patients, median  
179 (IQR) age and BMI were 44.7 years (38.5-51.8) and 32.8 kg/m<sup>2</sup> (31.1-35.4), respectively. Obese  
180 patients were more frequently women than men (59.8% versus 40.2%), and African ethnicity  
181 was the most represented (74.2%). Median (IQR) time from HIV infection diagnosis, time on  
182 ARV treatment, and time on current ARV treatment on the day of concentration assessment  
183 was 8 years (6-12), 6 years (3-10) and 1.5 years (0.6-2.4), respectively. First line therapy  
184 patients accounted for 21.3% of the obese patients. Virological success was observed in 88.3%  
185 of obese patients, and median (IQR) CD4<sup>+</sup> T-cell count was at 510 cells/ $\mu$ L (397-719).  
186 Demographic characteristics did not differ between obese and control patients, except for  
187 gender, with greater proportion of obese women (59.8% versus 42.3%,  $P < 0.001$ ). Median time  
188 from HIV infection diagnosis and time on ARV treatment was shorter for obese patients than  
189 controls (8 and 6 versus 10 and 8 years,  $P = 0.03$  and  $0.05$ , respectively), yet median time on  
190 current ARV treatment was longer (1.5 versus 0.9 years,  $P < 0.001$ ). The proportion of

191 virological success was similar in the 2 groups, but CD4+ T-cell count was higher for obese  
192 patients than controls (510 versus 444 cells/ $\mu$ L,  $P < 0.001$ ).

### 193 *ARV plasma concentrations*

194 To analyze the 12 ARVs, we assayed 881 plasma concentrations from obese patients and 585  
195 from controls. For each drug, at least 80% of patients received treatment according to French  
196 national recommendations:<sup>3,20</sup> 600 mg once daily for abacavir and efavirenz, 200 mg once daily  
197 for emtricitabine, 300 mg once daily for lamivudine and tenofovir disoproxil fumarate, 200 mg  
198 twice daily /400 mg once daily for etravirine, 200 mg twice daily for nevirapine, 400/100 mg  
199 twice daily for lopinavir associated with ritonavir, 300/100 mg once daily for atazanavir  
200 associated with ritonavir and 400 mg twice daily for raltegravir. For darunavir, the 2 dosing  
201 regimens associated with ritonavir, 800/100 mg once daily and 600/100 mg twice daily, were  
202 analyzed separately because of the short half-life of darunavir. Ritonavir concentrations were  
203 compared by dosing regimen, 100 mg twice daily and 100 mg once daily.

204 For the NRTIs, median (IQR) tenofovir C12h was lower by 23% for obese than normal-weight  
205 patients (66 ng/mL [48-84] versus 86 ng/mL [54-117],  $P < 0.001$ ). No significant difference  
206 was found for abacavir, emtricitabine and lamivudine. Tenofovir concentration difference was  
207 also significant for patients receiving tritherapy with two NRTI and one NNRTI ( $P = 0.013$ ),  
208 but not for patient treated with two NRTI and one PI ( $P = 0.11$ ) (Figure 3). For the NNRTIs,  
209 median (IQR) plasma C12h for efavirenz was lower, by 26%, for obese than control patients  
210 (1,498 ng/mL [1,091-2,292] versus 2,034 ng/mL [1,566-3,181],  $P < 0.001$ ) (Figure 2), with no  
211 significant difference for nevirapine and etravirine. For the PI, median plasma concentration  
212 for lopinavir was also lower, by 28%, for obese than control patients (4,595 ng/mL [3,446-  
213 6,136] versus 6,420 ng/mL [5,215-7,677],  $P < 0.001$ ), with no difference for atazanavir and  
214 darunavir (Figure 2). Ritonavir concentrations showed comparable discrepancies as lopinavir,

215 with median trough concentrations of 79 ng/mL (40-123) and 69 ng/mL (33-115) for obese  
216 patients and 256 ng/mL (150-370) and 162 ng/mL (50-303) for controls when administered 100  
217 mg twice daily and 100 mg once daily, respectively ( $P < 0.001$  and  $P < 0.001$ ). Finally, median  
218 C12h for raltegravir was 44% lower for obese than control patients (120 ng/mL [62-256] versus  
219 215 ng/mL [145-300]) but not significantly ( $P = 0.082$ ).

220 Obese patients showed plasma concentrations below the efficacy threshold depending on the  
221 ARV considered (Table 2), with proportions of patients  $> 15\%$  for efavirenz, nevirapine,  
222 etravirine and raltegravir and up to 24.4% for lopinavir. This suboptimal dosing was not present  
223 in the control group, with only one patient (2.5%) showing C24h  $< 550$  ng/mL with darunavir  
224 once daily. Proportions significantly differed between the 2 groups for efavirenz ( $P < 0.001$ )  
225 and lopinavir ( $P = 0.002$ ). For concentrations above toxicity threshold, controls did not differ  
226 from obese patients in concentrations being above the cutoff for the 5 drugs considered (Table  
227 2).

228 We found no major compliance issue in both groups; only 4 obese patients had undetectable  
229 concentrations for all ARV, for a probable lack of adherence.

### 230 ***Multivariate analysis***

231 All the available demographic and infection characteristics were included in the multivariate  
232 logistic regression models, except for time under ARV treatment, which was largely correlated  
233 with time since HIV diagnosis.

234 The risk of at least one ARV concentration being below the efficacy threshold was strongly  
235 associated with obesity (Table 3) (odds ratio [OR] 42.63 [95% CI 5.71-318.26]); the only other  
236 covariates associated with ARV concentration being below the efficacy threshold were time  
237 since HIV diagnosis (OR 0.89 [95% CI 0.83-0.97] per year) and receiving ARV tritherapy

238 which was not the association of two NRTI and one PI or two NRTI and one NNRTI (OR 3.36  
239 [95% CI 1.07-10.59]).

240 However, virological failure was not associated with obesity or ARV plasma concentration  
241 below the efficacy threshold at the day of sampling (OR 0.66 [95% CI 0.37-1.20] and 1.54  
242 [95% CI 0.63-3.76], respectively, after adjustment for other covariates) (Table 4). The 2  
243 variables associated were time since HIV infection diagnosis and time on current ARV  
244 treatment (OR 0.94 [95% CI 0.89-1.00] and 0.71 [95% 0.55-0.92] per year, respectively).  
245 Considering virological failure at one year after ARV plasma concentration assessment, we  
246 found no association with any of the variables included in the multivariate model (Table 4).

#### 247 *One-year follow-up and drug switch*

248 During the follow-up period, from the day of ARV concentration assessment to the end of the  
249 study period, 157 (54.0%) obese patients and 110 (56.1%) controls had at least one drug switch  
250 (Table 5), with no difference between the groups in proportion of switches ( $P = 0.71$ ), time  
251 before switch ( $P = 0.19$ ), BMI evolution ( $P = 0.18$ ), or virological failure at the time of the  
252 switch ( $P = 0.45$ ). However, reasons advocated by physicians for the switch differed between  
253 the groups (global chi-square test,  $P < 0.01$ ), with therapeutic simplification the most frequent  
254 cause for obese patients and occurrence of adverse events for controls.

## 255 **Discussion**

256 Here, we report for the first time the pharmacokinetics of several ARVs in obese HIV-infected  
257 patients in the context of usual medical care. Considering ARVs from NRTI, NNRTI, PI and  
258 integrase inhibitor classes, our study highlights significantly lower plasma concentrations in  
259 obese patients for tenofovir (-23%), efavirenz (-24%) and lopinavir (-28%) and a trend for  
260 raltegravir (-44%), for significantly greater proportion of infected obese patients with potential

261 inefficient drug exposure than infected normal-weight patients (17.5% versus 0.5%). However,  
262 we found no deleterious impact of this suboptimal dosing on this virologically controlled  
263 population, even one year after drug concentration assessment.

264 Obesity is known to alter the pharmacokinetics of numerous drugs. In our study, obesity affects  
265 plasma concentrations of 4 ARV: tenofovir, efavirenz, lopinavir and ritonavir. Although  
266 tenofovir is a hydrophilic molecule, its ester prodrug, tenofovir disoproxil, is far more lipophilic  
267 ( $\log P_{\text{octanol/water}}$  1.25). Low body weight was previously reported to be associated to high  
268 tenofovir plasma concentration in Caucasian women.<sup>27</sup> We reported here a similar association  
269 between concentration and BMI in obese population. Interestingly, this discrepancy seems  
270 reduced in patients receiving PI. This observation may be related to the renal drug-drug  
271 interaction described with PI, decreasing tenofovir clearance<sup>28</sup> and protect obese patients from  
272 concentration drop observed with other ARV. Efavirenz is a lipophilic drug ( $\log P_{\text{octanol/water}}$  4.6),  
273 with high binding to albumin (99.5%),<sup>29</sup> and demonstrates a high affinity for adipose tissue,  
274 with concentrations up to 100-fold higher than in plasma.<sup>10</sup> Underdosing was reported in  
275 patients with this drug.<sup>30,31</sup> Therefore, the obesity impact was expected, and an explanation  
276 might be the sequestration of drug in adipose tissue, thereby lowering plasma concentration and  
277 making it unavailable to target compartments. These results were more unexpected for lopinavir  
278 and may have different physiological causes. Even if lopinavir largely binds to plasma proteins  
279 and has high  $\log P_{\text{octanol/water}}$  (5.9), it undergoes fast metabolism mediated by cytochrome P450  
280 3A isoenzymes,<sup>32</sup> for a short half-life of 5 to 6 hr. Drugs of the same class were not found to  
281 accumulate in fat tissue,<sup>10</sup> yet a body weight effect was found in pregnant women<sup>33</sup> and  
282 children<sup>34</sup> for both distribution and clearance. Interestingly, ritonavir, closely related to  
283 lopinavir structurally, presented the same concentration pattern between our obese and normal-  
284 weight patients. Finally, we observed a trend for raltegravir in terms of reduced concentration  
285 in obese patients, associated with large variability, but the few number of patients receiving this

286 molecule ( $n < 30$ ) does not allow for robust conclusions. Raltegravir does not have a lipophilic  
287 profile ( $\log P_{\text{octanol/water}}$  0.4), but has reduced solubility in acid aqueous solution. Thus, its  
288 gastrointestinal absorption largely depends on gastric pH. Gastroesophageal reflux disease,  
289 affecting about 50% of obese patients,<sup>35</sup> may reduce the raltegravir bioavailability and further  
290 increase the large inter-individual variability in plasma concentrations.

291 The multivariate analysis found a strong effect of obesity on the risk of having concentration  
292 below threshold, reflecting the results of the univariate analysis. An explanation to the moderate  
293 effect of the time from HIV diagnosis may be that older patients receive lopinavir, for which  
294 concentrations were more often under threshold than for more recent PI darunavir and  
295 atazanavir.

296 Unfortunately, we were not able to include all the potential confounding factors which may  
297 impact ARV concentrations in this analysis. Genetics polymorphism on metabolism enzymes  
298 would have been of interest, for instance on CYP2B6, for which single nucleotide  
299 polymorphisms were described to affect efavirenz concentrations.<sup>36</sup> Close adherence  
300 measurement, as self-reporting or Medication Event Monitoring System, would also improve  
301 this work, yet these methods are not easily applied in routine practice because of cost  
302 effectiveness concern. Even if concentration assay might not be the most sensitive assessment,  
303 having only four patients with all concentrations below the LOQ made unlikely a major  
304 compliance issue in this study.

305 The high frequency of ARV concentrations below the efficacy threshold in obese patients was  
306 not associated with loss of virological control, either in the global cohort or in the subgroups  
307 receiving efavirenz or lopinavir (data not shown). This result should be cautioned considering  
308 that ARV cutoffs were defined for induction treatment, aiming to quickly decrease viral load in  
309 patients initiating treatment. The patients included in this study were in maintenance stage

310 (median of 7 years with current treatment) and may not require such stringent levels of  
311 concentration to control viral replication.

312 Both patient groups presented similar rates of virological failure on the day of drug assessment,  
313 after one year of follow-up, and at drug switch, for those who changed treatment. Virological  
314 control is multifactorial, depending notably on viral resistance and immunological background  
315 and considering treatment, observance and other ARVs administered. Immunological response  
316 was better for obese than normal-weight patients, as previously reported.<sup>1,11</sup> Overall, our results  
317 largely agree with those recently reported from a large cohort of patients receiving efavirenz,<sup>37</sup>  
318 showing that obesity does not affect virological and immunological response, despite potential  
319 reduced ARV exposure.

## 320 *Conclusions*

321 The increasing rate of obesity among HIV-infected patients requires adapted medical care. We  
322 showed that obesity affects the pharmacokinetics of three frequently prescribed ARVs,  
323 tenofovir, efavirenz and lopinavir; it lowers the plasma concentrations of the drugs and is likely  
324 to affect others ARV. In addition, the observed large variability in concentrations implies that  
325 some patients may be overdosed. An extension of this study to new ARV drugs recently  
326 available, such as dolutegravir, elvitegravir or rilpivirine, would be of interest. We did not  
327 demonstrate an impact of these concentrations on virological or immunological control, arguing  
328 that obese patients with maintenance ARV treatment would not suffer from this suboptimal  
329 exposure. However, these results may encourage drug therapeutic monitoring in this population  
330 at induction when plasma viral load is high, or when resistance mutations are present and higher  
331 therapeutic concentrations are needed.

332

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347

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- 449

Table 1.

Characteristics of obese and normal-weight controls at inclusion, corresponding to the day of drug concentration assessment.

Characteristic	Obese (n=291)		Normal-weight (n=196)		P*	
	No.	%	No.	%		
Age (years)	<40	91	31.3	59	30.1	0.47
	40-49	103	35.4	58	29.6	
	50-59	71	24.4	67	34.2	
	≥60	26	8.9	10	5.1	
Gender	Female	174	59.8	83	42.3	<b>0.00029</b>
	Male	117	40.2	113	57.7	
BMI (kg/m <sup>2</sup> )	20-25	0	0.0	196	100.0	<b>&lt;10<sup>-16</sup></b>
	30-35	207	71.1	0	0.0	
	36-40	61	21.0	0	0.0	
	>40	23	7.9	0	0.0	
Ethnicity	African	216	74.2	128	65.3	0.077
	Caucasian	32	11.0	38	19.4	
	Hispanic	20	6.9	17	8.7	
	Unknown	23	7.9	16	8.2	
First line therapy		62	21.3	48	24.5	0.44
Time from HIV diagnosis (years), median (IQR)		8	[6-12]	10	[5-17]	<b>0.029</b>
Time on ARV treatment (years), median (IQR)		6	[3-10]	8	[2-14]	0.050
Time on current ARV treatment (years), median (IQR)		1.5	[0.6-2.4]	0.9	[0.3-2.1]	<b>0.00014</b>
CD4+ T-cell count (cells/μL), median (IQR)		510	[397-719]	444	[267-602]	<b>0.00012</b>
Virological success		257	88.3	164	83.7	0.18
ARV treatment	2 NRTI + 1 PI	137	47.1	77	39.3	0.12

2 NRTI + 1 NNRTI	99	34.0	62	31.6
Other tri-therapy	22	7.6	22	11.2
Mono- or bi-therapy	12	4.1	14	7.1
Quadri- or penta-therapy	21	7.2	21	10.7

Data are no. (%) or median (interquartile range).

\* $P < 0.05$  by Fisher exact test for qualitative variables and Mann-Whitney test for quantitative variables.

NRTI, nucleoside reverse-transcriptase inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; ARV, antiretroviral; IQR, interquartile range

Table 2

Obese and normal-weight patient with ARV plasma concentration below the efficacy threshold (ARV may be inefficient) and above the toxicity threshold (ARV may be responsible for adverse events).

Drug	Plasma concentration < efficacy threshold					Plasma concentration > toxicity threshold				
	Obese		Normal-weight		<i>P</i> *	Obese		Normal-weight		<i>P</i> *
n	%	n	%	n		%	n	%		
<b>ETR</b>	4	21.1	0	0.0	0.12	7	36.8	5	35.7	1
<b>EFV</b>	15	19.2	0	0.0	<b>0.00039</b>	9	11.5	11	21.6	0.14
<b>NVP</b>	5	23.8	0	0.0	0.13	8	38.1	3	25.0	0.70
<b>LPV</b>	11	24.4	0	0.0	<b>0.0019</b>	5	11.1	8	24.2	0.14
<b>DRV QD</b>	6	12.8	1	2.5	0.12	–	–	–	–	–
<b>DRV BID</b>	0	0.0	0	0.0	–	–	–	–	–	–
<b>ATV</b>	6	9.0	0	0.0	0.17	26	38.8	12	41.4	0.82
<b>RAL</b>	5	17.9	0	0.0	0.053	–	–	–	–	–
<b>TFV</b>	–	–	–	–	–	5	3.1	12	10.3	0.024

EFV efavirenz, NVP nevirapine, ETR etravirine, LPV lopinavir, ATV atazanavir, DRV darunavir (QD, once a day; BID, twice a day), RAL raltegravir, TFV tenofovir. \**P* < 0.05 by Fisher exact test.

Table 3. Association between underdosing and obesity, adjusted by demographics and infection characteristics.

Characteristic		Patients with at least one ARV plasma concentration below therapeutic range (n=52)		Patients with plasma concentrations within therapeutic range (n=435)		OR	95% CI	P
		n	%	n	%			
<b>BMI (kg/m<sup>2</sup>), n (%)</b>	<25 kg/m <sup>2</sup>	1	0.5	195	99.5			
	≥30 kg/m <sup>2</sup>	51	17.5	240	82.5	42.6 3	[5.71-318.26]	<b>0.00025</b>
<b>Age (years), median (IQR)</b>	–	47.5	[37.9-51.5]	45.0	[38.0-52.1]	1.00	[0.96-1.03]	0.81
<b>Gender</b>	Female	30	11.7	227	88.3			
	Male	22	9.6	206	90.4	0.96	[0.43-2.11]	0.92
<b>Ethnicity</b>	African	38	11.1	305	88.9			
	Caucasian	8	11.6	61	88.4	1.78	[0.61-5.18]	0.29
	Hispanic	5	13.9	31	86.1	1.52	[0.45-5.12]	0.50
	Other	1	2.6	37	97.4	0.18	[0.02-1.57]	0.12
<b>Time from HIV diagnosis (years), median (IQR)</b>		6	[3.8-10]	9	[5.7-14.8]	0.89	[0.83-0.97]	<b>0.0064</b>
<b>Time on current ARV treatment (years), median (IQR)</b>		1.4	[0.6-2.2]	1.2	[0.4-2.3]	1.16	[0.95-1.41]	0.14
<b>Line of treatment</b>	First line	16	14.5	94	85.5			
	Experienced	36	9.5	341	90.5	0.74	[0.33-1.64]	0.46
<b>ARV treatment</b>	2 NRTI + 1 PI	20	9.5	190	90.5			
	2 NRTI + 1 NNRTI	21	13.3	137	86.7	1.60	[0.77-3.33]	0.21
	Other tritherapy	6	13.6	38	86.4	3.36	[1.07-10.59]	<b>0.038</b>
	Bitherapy	3	11.5	23	88.5	3.79	[0.84-17.11]	0.083
	Quadritherapy or more	2	4.1	47	95.9	0.63	[0.13-3.06]	0.57

OR, adjusted odds ratio; 95% CI, 95% confidence interval; IQR interquartile range

Table 4.

Association between virological failure and obesity at inclusion and at 1 year of follow-up adjusted on demographics and infection characteristics, and ARV plasma concentrations.

Characteristic	Day of sampling								1 year follow-up						
	Virological failure n= 66		Virological success n= 421		OR	95% CI	P	Virological failure n= 70		Virological success n= 387		OR*	95% CI	P	
n	%	n	%	n				%	n	%	n				%
BMI (kg/m <sup>2</sup> ), n (%)	<25 kg/m <sup>2</sup>	32	16.3	164	83.7	–	–	–	31	16.9	152	83.1	–	–	–
	≥30 kg/m <sup>2</sup>	34	11.7	257	88.3	0.66	[0.37-1.20]	0.18	39	14.2	235	85.8	0.69	[0.39-1.23]	0.20
Age (years), median (IQR)	42.9	[35.0-50.5]	46.1	[38.6-52.6]	0.99	[0.96-1.02]	0.57	46.5	[37.0-50.9]	45.0	[38.2-52.0]	1.00	[0.97-1.03]	0.89	
Gender	Female	31	12.1	226	87.9	–	–	–	39	16.0	204	84.0	–	–	–
	Male	35	15.4	193	84.6	1.79	[0.95-3.37]	0.072	31	14.6	181	85.4	1.11	[0.60-2.03]	0.75
Ethnicity	African	51	14.9	292	85.1	–	–	–	54	16.7	269	83.3	–	–	–
	Caucasian	8	11.6	61	88.4	0.67	[0.27-1.66]	0.39	7	10.9	57	89.1	0.53	[0.21-1.35]	0.18
	Hispanic	5	13.9	31	86.1	0.83	[0.28-2.49]	0.74	5	13.9	31	86.1	0.79	[0.27-2.28]	0.66
	Other	2	5.3	36	94.7	0.33	[0.07-1.49]	0.15	4	12.1	29	87.9	0.70	[0.22-2.17]	0.53
Time from HIV diagnosis (years), median (IQR)	7.5	[3.3-11.0]	9.0	[5.7-14.7]	0.94	[0.89-1.00]	<b>0.039</b>	9.0	[5.0-15.5]	9.0	[5.2-14.0]	1.01	[0.96-1.06]	0.73	
Time on current ARV treatment (years), median (IQR)	0.5	[0.2-1.5]	1.4	[0.5-2.4]	0.71	[0.55-0.92]	<b>0.011</b>	1.0	[0.4-2.2]	1.3	[0.4-2.3]	0.98	[0.82-1.17]	0.84	
Line of treatment	First line	14	12.7	96	87.3	–	–	–	11	10.7	92	89.3	–	–	–
	Experienced	52	13.8	325	86.2	1.78	[0.86-3.70]	0.12	59	16.8	292	83.2	1.61	[0.76-3.44]	0.21
ARV concentration	> efficacy threshold	57	13.1	378	86.9	–	–	–	60	14.4	357	85.6	–	–	–
	< efficacy threshold	9	17.6	42	82.4	1.54	[0.63-3.76]	0.35	10	20.4	39	79.6	1.70	[0.74-3.93]	0.21

OR, adjusted odds ratio; 95% CI, 95% confidence interval; IQR interquartile range



Table 5.

Characteristics of patients at 1 year of follow-up and at drug switch.

Characteristics	Obese (n=291)		Normal-weight (n=196)		P*	
	n	%	n	%		
<b>At 1 year follow-up</b>						
Lost to follow-up	13	4.5	14	7.1	0.23	
Virological success	235	85.8	152	83.1	0.43	
Virological failure	39	14.2	31	16.9		
Drug switch	51	18.3	49	26.9	<b>0.037</b>	
Difference in BMI, median (IQR)	0	[-0.9-1.2]	0.3	[-0.4-1.0]	0.12	
Median time of follow-up (years), median (IQR)	4.06	[3.8-4.3]	4.28	[3.66-5.0]	<b>0.00093</b>	
<b>Drug switched</b>						
Patients with at least one switch	157	54.0	110	56.1	0.71	
Median time before switch (years), median (IQR)	1.58	[0.6-2.9]	1.29	[0.42-2.81]	0.19	
Difference in BMI at switch, median (IQR)	0	[-0.95-1.3]	0.3	[-0.38-1.3]	0.18	
Virological success at switch	126	80.3	84	76.4	0.45	
Virological failure at switch	31	19.7	26	23.6		
Reason for switch						
	Virological failure	22	13.8	21	18.9	<b>0.0089</b>
	Adverse events	35	22.0	38	34.2	
	Non observance	8	5.0	10	9.0	
	Toxicity prevention	25	15.7	5	4.5	
	Therapeutic simplification	50	31.4	26	23.4	
	Others	19	11.9	11	9.9	
Type of switch						
	Addition of drug	10	6.4	4	3.8	0.16
	Removal of drug	18	11.5	13	12.3	
	Change within the same class	51	32.5	48	45.3	

PI to NNRTI	25	15.9	8	7.5
PI to integrase inhibitor	11	7.0	3	2.8
NNRTI to PI	9	5.7	10	9.4
NNRTI to integrase inhibitor	10	6.4	6	5.7
Other class change	23	14.6	14	13.2

\*P < 0.05 by Fisher exact test for qualitative variables, except for the reasons for switch, which were compared by chi-square test, and Mann-Whitney test for quantitative variables. Other reasons for switch included pregnancy, protocol inclusion or end, drug interaction and not defined.

## Figure captions:

Figure 1: Flow chart of the retrospective study.

Figure 2: Trough plasma concentrations of etravirine (ETR), nevirapine (NVP), lopinavir (LPV), darunavir once daily and twice daily (DRV QD and DRV BID), atazanavir (ATV) and raltegravir (RAL), and C12h concentrations of efavirenz (EFV), abacavir (ABC), lamivudine (3TC), emtricitabine (FTC) and tenofovir (TFV) of in obese (dark grey) and normal-weight (light gray) patients. Number of patients (upper part of boxplot) and median concentration (lower part of boxplot) are reported for each group. P values at the top are from Mann-Whitney test comparing obese and normal-weight patients for each drug. The dash lines represent the efficacy thresholds for each ARV.

Figure 3: C12h concentrations of tenofovir, when associated to another nucleoside reverse transcriptase inhibitor and one protease inhibitor (left), or associated to another nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor (right). Number of patients (upper part of boxplot) and median concentration (lower part of boxplot) are reported for each group. P values at the top are from Mann-Whitney test comparing obese and normal-weight patients. PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, NRTI: nucleoside reverse transcriptase inhibitor.

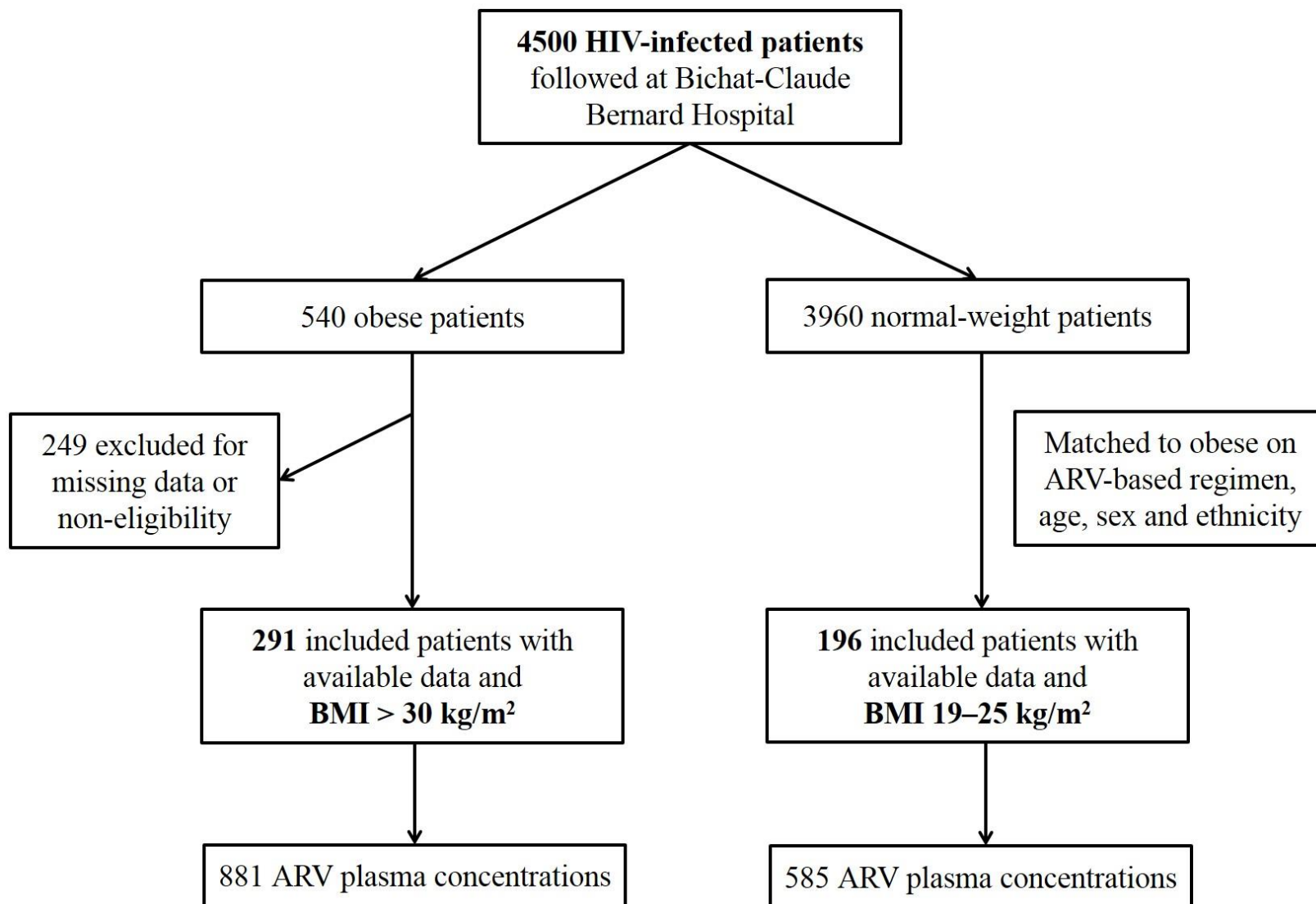


Figure 1

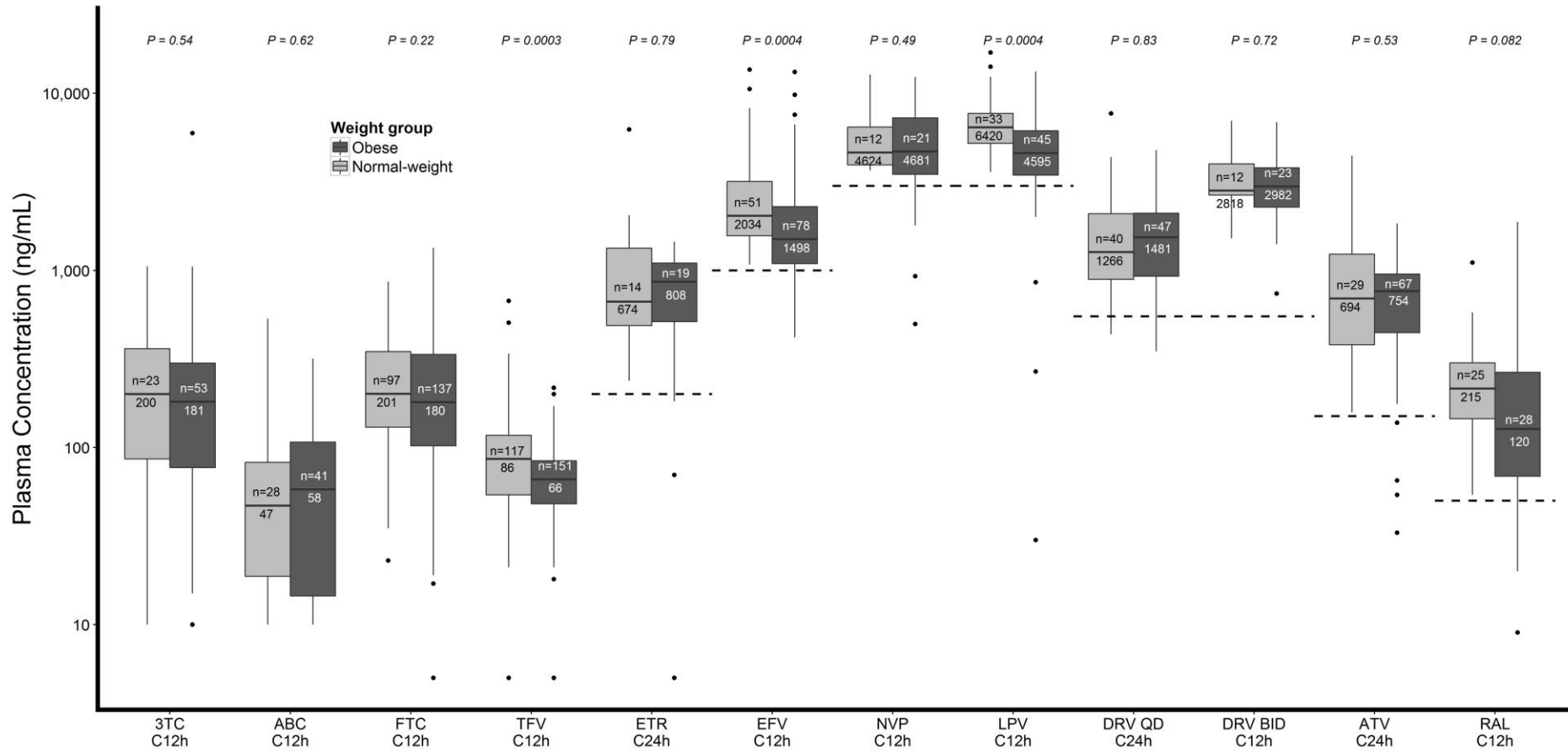


Figure 2

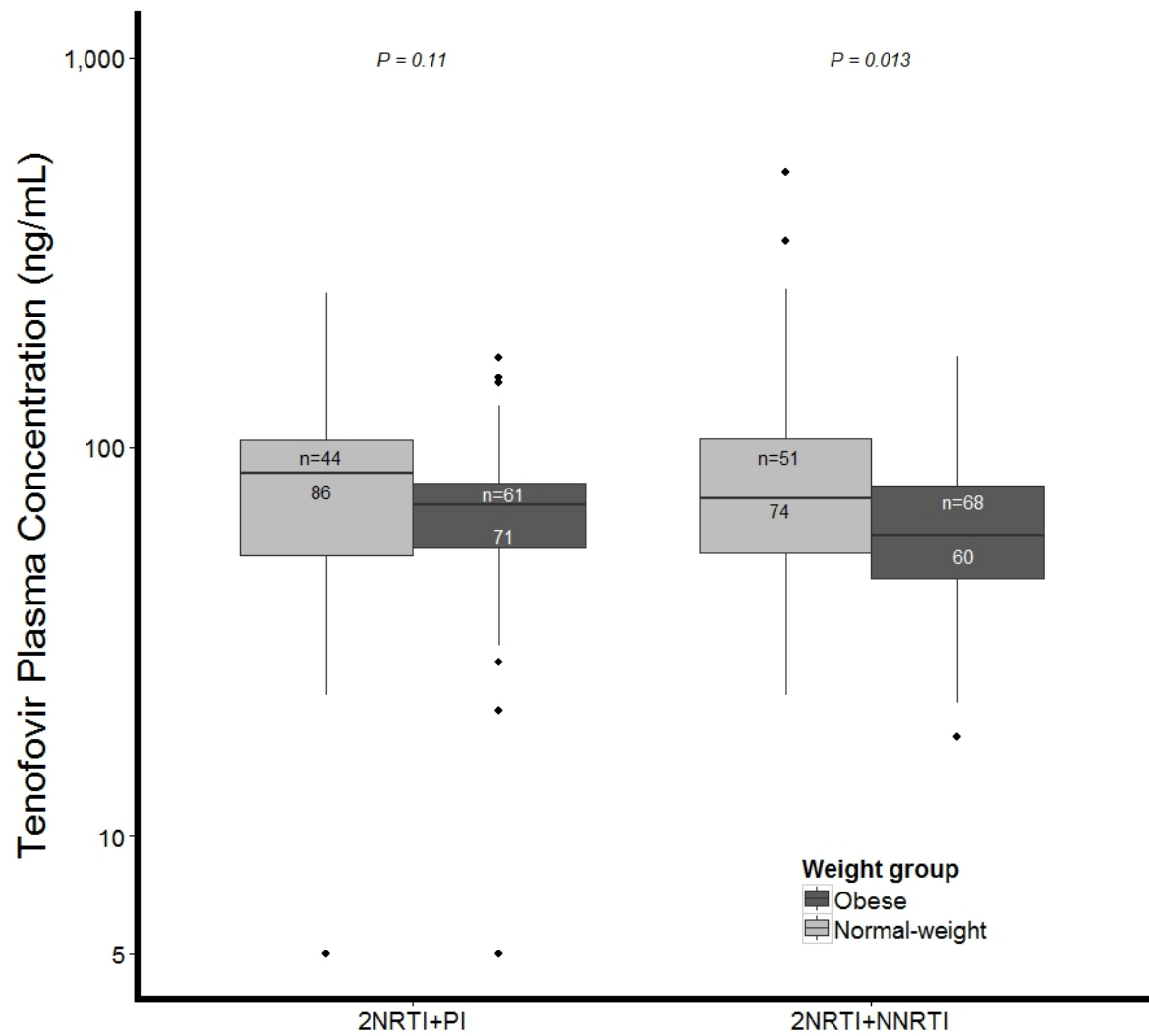


Figure 3