

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**
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16 **Running title:** Obesity and antiretroviral pharmacokinetics

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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) ≥ 30 kg/m² and normal-weight patients with BMI 19–25 kg/m². Plasma
34 concentrations (C_{12/24h}) 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_{12h} 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_{12/24h} 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/ μ 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.^{1,2} 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,³ thereby leading to global aging of the HIV-infected population.⁴
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.² Third, the increase in obesity is a worldwide
56 multifactorial trend, due to increased calories intake and lifestyle evolution.⁵

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 people⁶ affecting the
60 body disposition of numerous therapeutic agents and therefore plasma concentrations, related
61 in most cases to the drug activity.^{7,8} 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.⁹
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.¹⁰ 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,^{1,11} and show lower risk of evolution to AIDS.^{12,13} 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.^{14,15} 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,¹⁰ although a recent study demonstrated potential implications for the tissue as
78 a viral reservoir in HIV latency.¹⁶ However, fat tissue widely contributes to an inflammatory
79 state, with a notably large release of cytokines.^{17,18} If this continuous inflammation may play a
80 role in immunological control, it can lead to atherosclerosis and an increase in cardiovascular
81 events.¹⁹

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,^{3,20} 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) ≥ 30 kg/m²
102 according to the WHO definition⁵ who matched study eligibility criteria (Figure 1). Normal-
103 weight patients were defined with BMI 19 to 25 kg/m². 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/m² 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 ± 2 or 24 ± 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.²¹ 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 recommendations⁹ for atazanavir, efavirenz and nevirapine (150; 1,000 and 3,000 ng/mL,
141 respectively) or from clinical study²²⁻²⁵, 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.³ For tenofovir C12h, a toxicity threshold
147 was previously determined at 160 ng/mL.²⁶

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.²⁰ For obese patients, median
179 (IQR) age and BMI were 44.7 years (38.5-51.8) and 32.8 kg/m² (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⁺ T-cell count was at 510 cells/ μ 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/ μ 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:^{3,20} 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.²⁷ 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 clearance²⁸ 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%),²⁹ and demonstrates a high affinity for adipose tissue,
274 with concentrations up to 100-fold higher than in plasma.¹⁰ Underdosing was reported in
275 patients with this drug.^{30,31} 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,³² for a short half-life of 5 to 6 hr. Drugs of the same class were not found to
281 accumulate in fat tissue,¹⁰ yet a body weight effect was found in pregnant women³³ and
282 children³⁴ 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,³⁵ 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.³⁶ 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.^{1,11} Overall, our results
317 largely agree with those recently reported from a large cohort of patients receiving efavirenz,³⁷
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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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 | 0.00029 |
| | Male | 117 | 40.2 | 113 | 57.7 | |
| BMI (kg/m ²) | 20-25 | 0 | 0.0 | 196 | 100.0 | <10⁻¹⁶ |
| | 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] | 0.029 |
| 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] | 0.00014 |
| CD4+ T-cell count (cells/μL), median (IQR) | | 510 | [397-719] | 444 | [267-602] | 0.00012 |
| 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).

| | Plasma concentration < efficacy threshold | | | | | Plasma concentration > toxicity threshold | | | | |
|----------------|---|------|---------------|-----|----------------|---|------|---------------|------|------------|
| | Obese | | Normal-weight | | <i>P</i> * | Obese | | Normal-weight | | <i>P</i> * |
| Drug | n | % | n | % | | n | % | n | % | |
| ETR | 4 | 21.1 | 0 | 0.0 | 0.12 | 7 | 36.8 | 5 | 35.7 | 1 |
| EFV | 15 | 19.2 | 0 | 0.0 | 0.00039 | 9 | 11.5 | 11 | 21.6 | 0.14 |
| NVP | 5 | 23.8 | 0 | 0.0 | 0.13 | 8 | 38.1 | 3 | 25.0 | 0.70 |
| LPV | 11 | 24.4 | 0 | 0.0 | 0.0019 | 5 | 11.1 | 8 | 24.2 | 0.14 |
| DRV QD | 6 | 12.8 | 1 | 2.5 | 0.12 | – | – | – | – | – |
| DRV BID | 0 | 0.0 | 0 | 0.0 | – | – | – | – | – | – |
| ATV | 6 | 9.0 | 0 | 0.0 | 0.17 | 26 | 38.8 | 12 | 41.4 | 0.82 |
| RAL | 5 | 17.9 | 0 | 0.0 | 0.053 | – | – | – | – | – |
| TFV | – | – | – | – | – | 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 | % | | | |
| BMI (kg/m²), n (%) | <25 kg/m ² | 1 | 0.5 | 195 | 99.5 | | | |
| | ≥30 kg/m ² | 51 | 17.5 | 240 | 82.5 | 42.6 3 | [5.71-318.26] | 0.00025 |
| Age (years), median (IQR) | – | 47.5 | [37.9-51.5] | 45.0 | [38.0-52.1] | 1.00 | [0.96-1.03] | 0.81 |
| Gender | Female | 30 | 11.7 | 227 | 88.3 | | | |
| | Male | 22 | 9.6 | 206 | 90.4 | 0.96 | [0.43-2.11] | 0.92 |
| Ethnicity | 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 |
| Time from HIV diagnosis (years), median (IQR) | | 6 | [3.8-10] | 9 | [5.7-14.8] | 0.89 | [0.83-0.97] | 0.0064 |
| Time on current ARV treatment (years), median (IQR) | | 1.4 | [0.6-2.2] | 1.2 | [0.4-2.3] | 1.16 | [0.95-1.41] | 0.14 |
| Line of treatment | First line | 16 | 14.5 | 94 | 85.5 | | | |
| | Experienced | 36 | 9.5 | 341 | 90.5 | 0.74 | [0.33-1.64] | 0.46 |
| ARV treatment | 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] | 0.038 |
| | 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 ²), n (%) | <25 kg/m ² | 32 | 16.3 | 164 | 83.7 | – | – | – | 31 | 16.9 | 152 | 83.1 | – | – | – |
| | ≥30 kg/m ² | 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] | 0.039 | 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] | 0.011 | 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 | % | | |
| At 1 year follow-up | | | | | | |
| 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 | 0.037 | |
| 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] | 0.00093 | |
| Drug switched | | | | | | |
| 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 | 0.0089 |
| | 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.

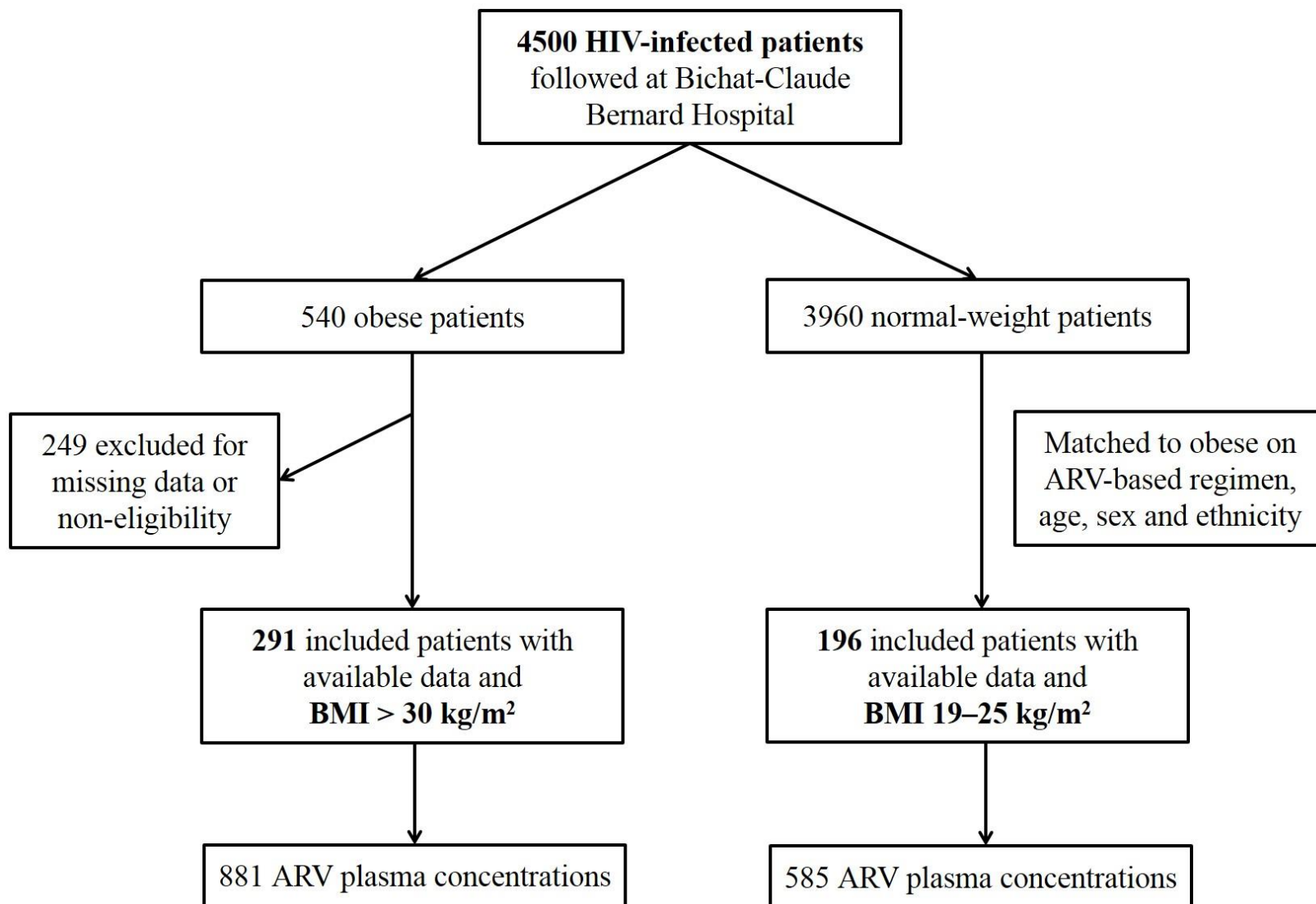


Figure 1

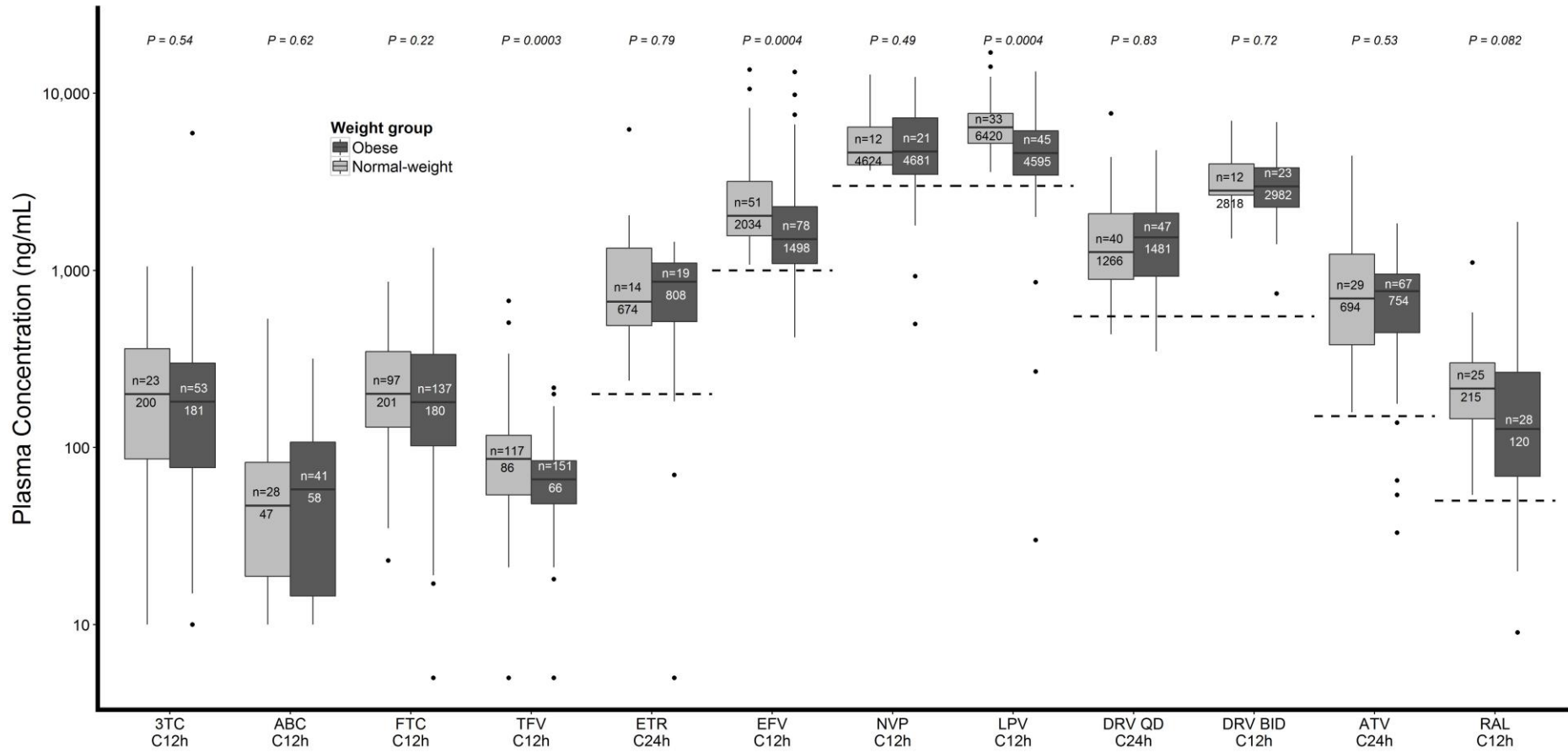


Figure 2

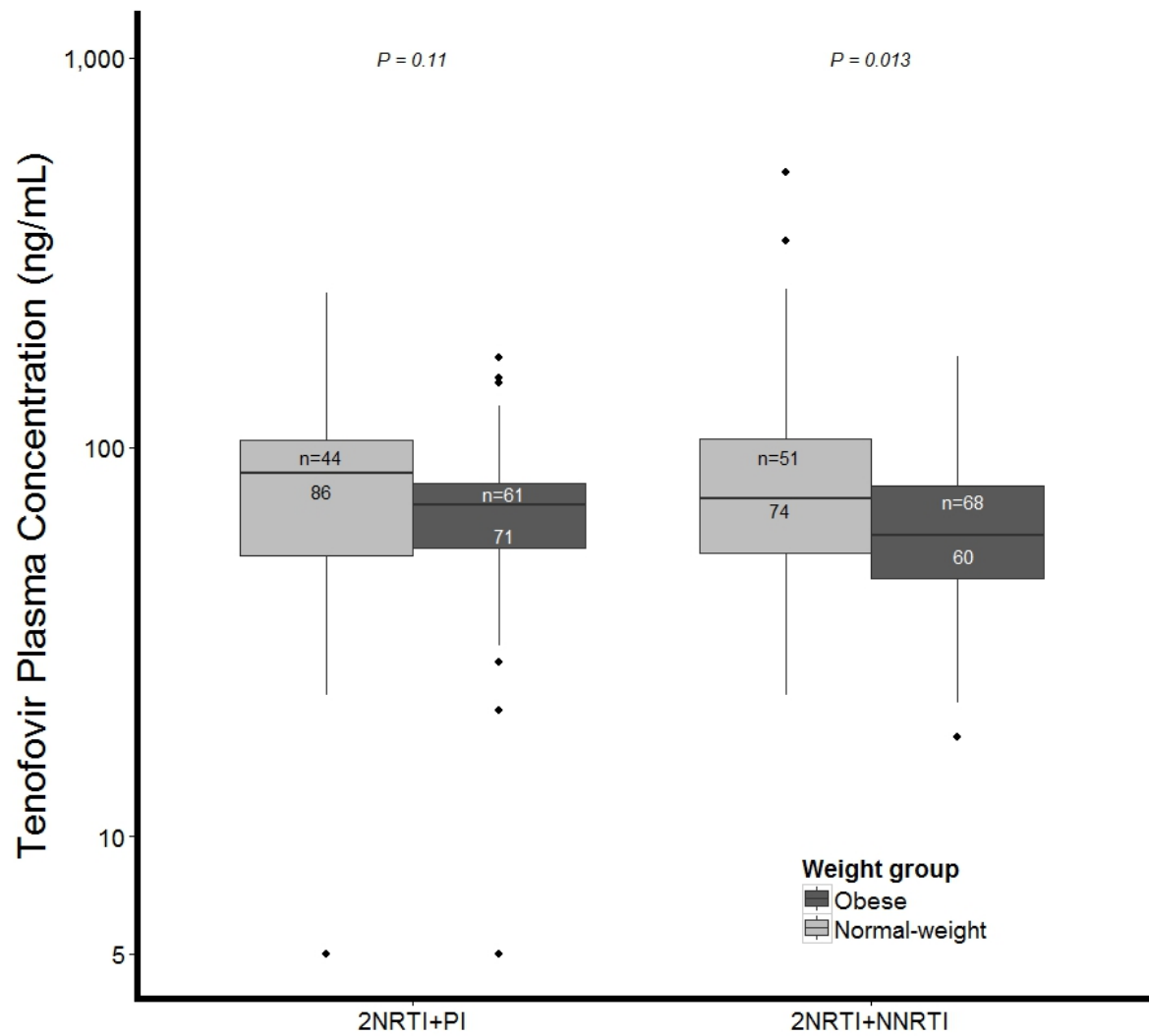


Figure 3