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

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ABSTRACT:

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

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

Patients and methods: We examined data from 2009 to 2012 in our hospital's database for HIV-1-infected patients who received an antiretroviral drug among abacavir, emtricitabine, lamivudine, tenofovir, efavirenz, etravirine, nevirapine, atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir and raltegravir. Obese patients were defined with body mass index (BMI) ≥30 kg/m^2 and normal-weight patients with BMI 19–25 kg/m^2. Plasma concentrations (C12/24h) were compared for each antiretroviral using Mann-Whitney test. Suboptimal dosing and virological outcome were assessed by logistic regression, adjusting on covariates.

Results: We enrolled 291 obese and 196 normal-weight patients. Among the 12 analyzed antiretroviral drugs, tenofovir, efavirenz and lopinavir C12h were significantly lower in obese than normal-weight patients: 66 versus 86 ng/mL, 1,498 versus 2,034 ng/mL and 4,595 versus 6,420 ng/mL respectively ($P < 0.001$). Antiretroviral C12/24h were more frequently below efficacy thresholds for obese than normal-weight patients after adjustment for other covariates ($P < 0.001$). Although obese patients showed higher CD4 count than normal-weight (510 vs 444 cells/µL, $P < 0.001$), the groups did not differ in virological failure rate.

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

Introduction

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

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

Obese patients living with HIV, in addition, show a specific response to the infection. Several studies have reported that non-treated obese or overweight patients show better immunological control than normal-weight patients, with CD4+ T-cell count remaining higher despite similar control of plasma viral load,[1,11] and show lower risk of evolution to AIDS.[12,13] This superior immunological control was also found in obese patients receiving treatment, with faster recovery of CD4+ T-cell count after ARV initiation than in normal-weight patients.[14,15] Yet, the physiological features of this protection conferred by obesity are not well understood. Adipose tissue is not a favored site of HIV replication, with little recovery of viral RNA and integrated DNA,[10] although a recent study demonstrated potential implications for the tissue as a viral reservoir in HIV latency.[16] However, fat tissue widely contributes to an inflammatory state, with a notably large release of cytokines.[17,18] If this continuous inflammation may play a role in immunological control, it can lead to atherosclerosis and an increase in cardiovascular events.[19]

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

Patients and methods

Patients

Source population was HIV-1-infected patients followed from January 2009 to December 2012 in the university hospital Bichat-Claude Bernard, Paris for whom data were collected and available in the hospital electronic database. Patients were followed according to the French recommendations,[3,20] with viral load measurement and CD4+ T-cells count frequencies between 3 and 6 months. Therapeutic drug monitoring was commonly performed 15 to 30 days after introduction of new drug for various indications, as potential drug-drug interactions, adverse event, virological failure, abnormal BMI or malabsorption suspicion.

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

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

Ethics

All patients enrolled in this study gave their written informed consent to have their medical chart recorded in the electronic medical record system NADIS (Fedialis Medica, Marly Le Roi, France, French National Commission on Informatics and Rights CNIL approval no. 1171457 May 24, 2006, http://www.nadis.fr/), designed for the medical follow-up of HIV-infected patients, which also included their agreement to participate in retrospective studies.

ARV plasma concentration determination

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

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

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

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

Immuno-virological assessment

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

Statistical analysis

Data are reported as median and interquartile range (IQR: 25-75%). Demographic and infection characteristics were compared between obese and control group using Fisher exact test for categorical variable and non-parametric Mann-Whitney test for continuous variables. Plasma concentrations for each ARV drug were compared by Mann-Whitney test. Proportions of patients with concentrations below the efficacy threshold or above the toxicity threshold were compared for each drug, except ritonavir, abacavir, lamivudine and emtricitabine, by Fisher exact test. Multivariate logistic regression analysis was performed to explore the association of suboptimal dosing (defined as at least one ARV plasma concentration below the efficacy threshold) and virological failure with obesity, on the day of concentration assessment and at one year of follow-up, adjusting on demographic and infection characteristics. Because of the few control patients included, matching was not considered for statistical analysis. Statistical analysis was performed using R software v3.2.2. (https://cran.r-project.org/).

Results

Patients

We identified 540 HIV-1 infected obese patients among the 4,500 usually followed at Bichat-Claude Bernard Hospital; 291 of them matched the study eligibility criterions and were included (Figure 1, Table 1). We included 196 normal-weight matched patients. We were unable to include controls for each selected obese patient because of the demographic characteristics of patients followed at Bichat-Claude Bernard hospital and in particular the large prevalence of obesity in African women, added to the fact that concentration assays were not systematic for normal weight patients, according to the French recommendations.[20] For obese patients, median (IQR) age and BMI were 44.7 years (38.5-51.8) and 32.8 kg/m^2 (31.1-35.4), respectively. Obese patients were more frequently women than men (59.8% versus 40.2%), and African ethnicity was the most represented (74.2%). Median (IQR) time from HIV infection diagnosis, time on ARV treatment, and time on current ARV treatment on the day of concentration assessment was 8 years (6-12), 6 years (3-10) and 1.5 years (0.6-2.4), respectively. First line therapy patients accounted for 21.3% of the obese patients. Virological success was observed in 88.3% of obese patients, and median (IQR) CD4+ T-cell count was at 510 cells/µL (397-719). Demographic characteristics did not differ between obese and control patients, except for gender, with greater proportion of obese women (59.8% versus 42.3%, $P < 0.001$). Median time from HIV infection diagnosis and time on ARV treatment was shorter for obese patients than controls (8 and 6 versus 10 and 8 years, $P = 0.03$ and 0.05, respectively), yet median time on current ARV treatment was longer (1.5 versus 0.9 years, $P < 0.001$). The proportion of virological success was similar in the 2 groups, but CD4+ T-cell count was higher for obese patients than controls (510 versus 444 cells/µL, $P < 0.001$).

ARV plasma concentrations

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

For the NRTIs, median (IQR) tenofovir C12h was lower by 23% for obese than normal-weight patients (66 ng/mL [48-84] versus 86 ng/mL [54-117], P < 0.001). No significant difference was found for abacavir, emtricitabine and lamivudine. Tenofovir concentration difference was also significant for patients receiving tritherapy with two NRTI and one NNRTI ($P = 0.013$), but not for patient treated with two NRTI and one PI ($P = 0.11$) (Figure 3). For the NNRTIs, median (IQR) plasma C12h for efavirenz was lower, by 26%, for obese than control patients (1,498 ng/mL [1,091-2,292] versus 2,034 ng/mL [1,566-3,181], $P < 0.001$) (Figure 2), with no significant difference for nevirapine and etravirine. For the PI, median plasma concentration for lopinavir was also lower, by 28%, for obese than control patients (4,595 ng/mL [3,446-6,136] versus 6,420 ng/mL [5,215-7,677], $P < 0.001$), with no difference for atazanavir and darunavir (Figure 2). Ritonavir concentrations showed comparable discrepancies as lopinavir, with median trough concentrations of 79 ng/mL (40-123) and 69 ng/mL (33-115) for obese patients and 256 ng/mL (150-370) and 162 ng/mL (50-303) for controls when administered 100 mg twice daily and 100 mg once daily, respectively ($P < 0.001$ and $P < 0.001$). Finally, median C12h for raltegravir was 44% lower for obese than control patients (120 ng/mL [62-256] versus 215 ng/mL [145-300]) but not significantly ($P = 0.082$).

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

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

Multivariate analysis

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

The risk of at least one ARV concentration being below the efficacy threshold was strongly associated with obesity (Table 3) (odds ratio [OR] 42.63 [95% CI 5.71-318.26]); the only other covariates associated with ARV concentration being below the efficacy threshold were time since HIV diagnosis (OR 0.89 [95% CI 0.83-0.97] per year) and receiving ARV tritherapy which was not the association of two NRTI and one PI or two NRTI and one NNRTI (OR 3.36 [95% CI 1.07-10.59]).

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

One-year follow-up and drug switch

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

Discussion

Here, we report for the first time the pharmacokinetics of several ARVs in obese HIV-infected patients in the context of usual medical care. Considering ARVs from NRTI, NNRTI, PI and integrase inhibitor classes, our study highlights significantly lower plasma concentrations in obese patients for tenofovir (-23%), efavirenz (-24%) and lopinavir (-28%) and a trend for raltegravir (-44%), for significantly greater proportion of infected obese patients with potential inefficient drug exposure than infected normal-weight patients (17.5% versus 0.5%). However, we found no deleterious impact of this suboptimal dosing on this virologically controlled population, even one year after drug concentration assessment.

Obesity is known to alter the pharmacokinetics of numerous drugs. In our study, obesity affects plasma concentrations of 4 ARV: tenofovir, efavirenz, lopinavir and ritonavir. Although tenofovir is a hydrophilic molecule, its ester prodrug, tenofovir disoproxil, is far more lipophilic ($\log P_{octanol/water}$ 1.25). Low body weight was previously reported to be associated to high tenofovir plasma concentration in Caucasian women.[27] We reported here a similar association between concentration and BMI in obese population. Interestingly, this discrepancy seems reduced in patients receiving PI. This observation may be related to the renal drug-drug interaction described with PI, decreasing tenofovir clearance[28] and protect obese patients from concentration drop observed with other ARV. Efavirenz is a lipophilic drug ($\log P_{octanol/water}$ 4.6), with high binding to albumin (99.5%),[29] and demonstrates a high affinity for adipose tissue, with concentrations up to 100-fold higher than in plasma.[10] Underdosing was reported in patients with this drug.[30,31] Therefore, the obesity impact was expected, and an explanation might be the sequestration of drug in adipose tissue, thereby lowering plasma concentration and making it unavailable to target compartments. These results were more unexpected for lopinavir and may have different physiological causes. Even if lopinavir largely binds to plasma proteins and has high $\log P_{octanol/water}$ (5.9), it undergoes fast metabolism mediated by cytochrome P450 3A isoenzymes,[32] for a short half-life of 5 to 6 hr. Drugs of the same class were not found to accumulate in fat tissue,[10] yet a body weight effect was found in pregnant women[33] and children[34] for both distribution and clearance. Interestingly, ritonavir, closely related to lopinavir structurally, presented the same concentration pattern between our obese and normal-weight patients. Finally, we observed a trend for raltegravir in terms of reduced concentration in obese patients, associated with large variability, but the few number of patients receiving this molecule (n<30) does not allow for robust conclusions. Raltegravir does not have a lipophilic profile ($logP_{octanol/water}$ 0.4), but has reduced solubility in acid aqueous solution. Thus, its gastrointestinal absorption largely depends on gastric pH. Gastroesophageal reflux disease, affecting about 50% of obese patients,[35] may reduce the raltegravir bioavailability and further increase the large inter-individual variability in plasma concentrations.

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

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

The high frequency of ARV concentrations below the efficacy threshold in obese patients was not associated with loss of virological control, either in the global cohort or in the subgroups receiving efavirenz or lopinavir (data not shown). This result should be cautioned considering that ARV cutoffs were defined for induction treatment, aiming to quickly decrease viral load in patients initiating treatment. The patients included in this study were in maintenance stage (median of 7 years with current treatment) and may not require such stringent levels of concentration to control viral replication.

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

Conclusions

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

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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			Obese		Normal-weight		
Drug	n	%	n	%	*P**	n	%	n	%	*P**
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)				
		n	%	n	%	OR	95% CI	*P*
BMI (kg/m2), n (%)	<25 kg/m^2	1	0.5	195	99.5			
	≥30 kg/m^2	51	17.5	240	82.5	42.63	[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.

		Day of sampling							1 year follow-up						
Characteristic		**Virological failure n= 66**		**Virological success n= 421**					**Virological failure n= 70**		**Virological success n= 387**				
		n	%	n	%	OR	95% CI	*P*	n	%	n	%	OR*	95% CI	*P*
BMI (kg/m2), n (%)	<25 kg/m^2	32	16.3	164	83.7	_	_	_	31	16.9	152	83.1	_	_	_
	$\geq$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.

		Obese (n=291)		**Normal-weight (n=196)**		
Characteristics		**n**	**%**	**n**	**%**	***P****
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.

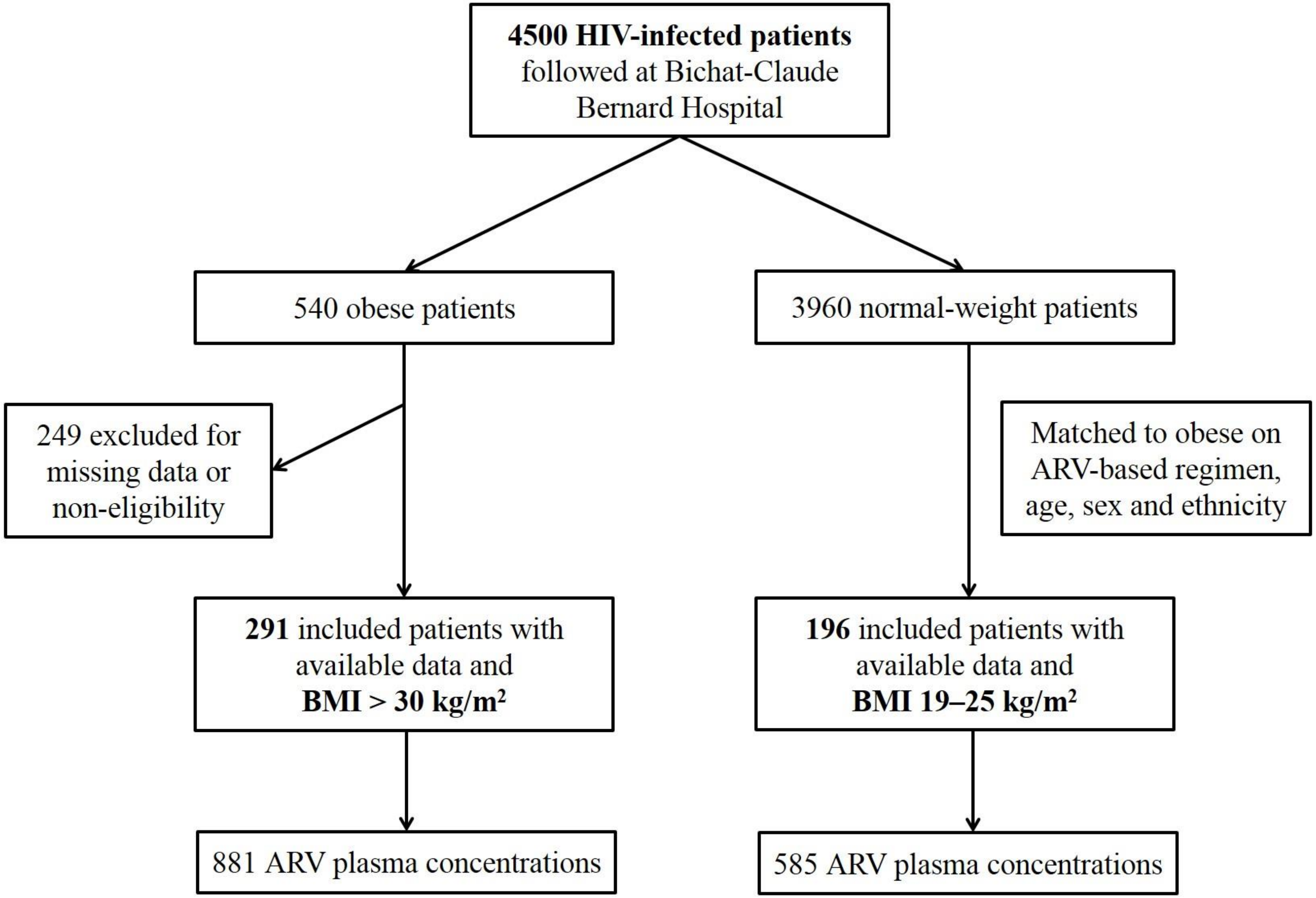
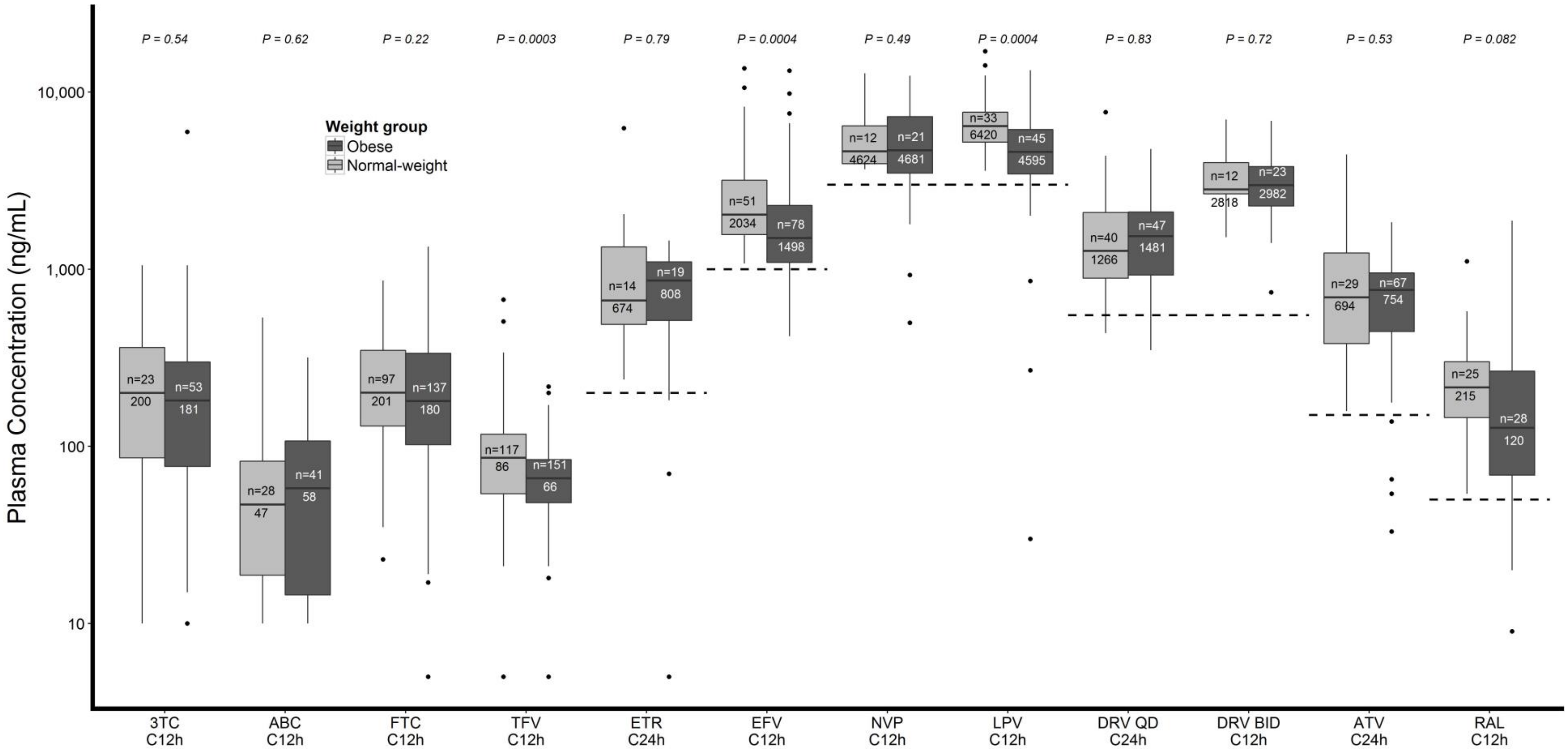
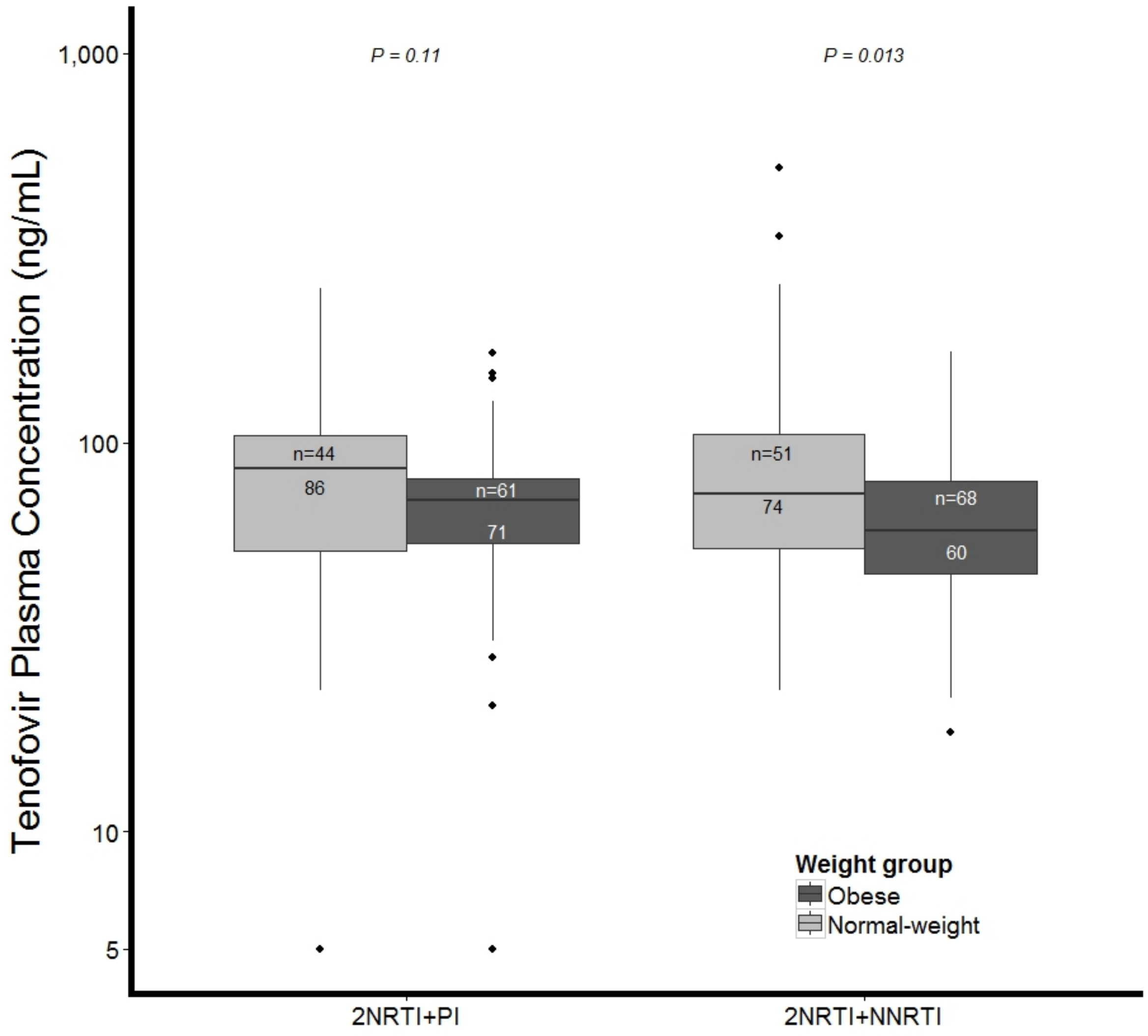

4500 HIV-infected patients followed at Bichat-Claude Bernard Hospital
540 obese patients
3960 normal-weight patients
249 excluded for missing data or non-eligibility
Matched to obese on ARV-based regimen, age, sex and ethnicity
291 included patients with available data and BMI > 30 kg/m²
196 included patients with available data and BMI 19–25 kg/m²
881 ARV plasma concentrations
585 ARV plasma concentrations

Figure 1



P = 0.54
P = 0.62
P = 0.22
P = 0.0003
P = 0.79
P = 0.0004
P = 0.49
P = 0.0004
P = 0.83
P = 0.72
P = 0.53
P = 0.082
Plasma Concentration (ng/mL)
10,000
1,000
100
10
Weight group
Obese
Normal-weight
n=23
200
n=53
181
n=28
47
n=41
58
n=97
201
n=137
180
n=117
86
n=151
66
n=14
674
n=19
808
n=51
2034
n=78
1498
n=12
4624
n=21
4681
n=33
6420
n=45
4595
n=40
1266
n=47
1481
n=12
2818
n=23
2982
n=29
694
n=67
754
n=25
215
n=28
120
3TC C12h
ABC C12h
FTC C12h
TFV C12h
ETR C24h
EFV C12h
NVP C12h
LPV C12h
DRV QD C24h
DRV BID C12h
ATV C24h
RAL C12h

Figure 2



P = 0.11
P = 0.013
1,000
100
10
5
Tenofovir Plasma Concentration (ng/mL)
n=44
86
n=61
71
n=51
74
n=68
60
Weight group
Obese
Normal-weight
2NRTI+PI
2NRTI+NNRTI

Figure 3