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SYNOPSIS

Introduction: Many studies have reported weight gain in ART-naïve people living with HIV (PWH) initiating an integrase strand-transfer inhibitor-based regimen. We studied the impact of early or advanced presentation and that of individual drugs in PWH initiating combined ART (cART) between 2012 and 2018.

Methods: From the French Hospital Database on HIV cohort, we assessed factors associated with a weight gain≥10%, weight change after cART initiation or BMI increase≥5kg/m^2 up to 30 months. The analyses were conducted overall, among PWH with early (primary infection or CD4>350/mm^3 and viral load<100000 copies/mL, without AIDS), and advanced presentation (AIDS or CD4<200/mm^3, not during primary infection).

Results: At 30 months, 34.5% (95%CI 33.5-35.6) of the 12,773 PWH had a weight gain≥10%, 20.9% (95%CI 19.6-22.2) among the 5,794 with early presentation and 63.1% (95%CI 60.9-65.3) among the 3,106 with advanced presentation. Weight gain was 2.8 kg (95% confidence-interval (CI) 2.0-3.7) for those with early presentation and 9.7 kg (95%CI 8.4-11.1) for those with advanced presentation. Most weight gain occurred in the first 12 months. Underweight and obese PWH were at significantly higher risk of BMI increase≥5kg/m^2 than normal-weight PWH. Results differed within classes and by outcome. Raltegravir and dolutegravir were consistently associated with greater weight gain than the other third agents. Tenofovir-alafenamide was also associated with higher weight gain than tenofovir-disoproxil or abacavir.

Discussion: After initiating cART, PWH with early presentation exhibited a small weight gain, whereas it was large among those with advanced presentation. The choice of ART should account for the risk of weight gain, especially for PWH who present with advanced disease and/or are obese.

INTRODUCTION

In recent recommendations for people living with HIV (PWH),[1, 2] the antiretroviral combination prescribed at initiation should include an integrase strand-transfer inhibitor (INSTI). However, two clinical trials conducted in sub-Saharan Africa (SSA) reported greater weight gain with dolutegravir than efavirenz, especially with dolutegravir combined with tenofovir, alafenamide, and emtricitabine (TAF/FTC).[3-5] Among studies conducted in high-income countries, many observational studies and pooled analyses of clinical trials have assessed the impact of treatment initiation on weight gain by the class of the third agent and found greater weight gain with INSTIs than non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and divergent results with protease inhibitors (PIs).[6-9] Only a small number of studies have assessed specific drugs.[10] Differences in weight gain between INSTIs were found but also similar weight gain.[6-11] Greater weight gain was observed with TAF/FTC than with tenofovir disoproxil and emtricitabine (TDF/FTC)[7, 8, 10, 11]. In parallel, recent studies have shown the capacity of dolutegravir and raltegravir to induce adipocyte hypertrophy, adipose tissue fibrosis, and insulin resistance.[12-14] Weight gain in PWH raises concerns about the potential associated increased risk of cardiovascular and metabolic diseases and mortality[15, 16]. A large meta-analysis in the general population showed that an increase in body-mass index (BMI) of 5 kg/m^2 is associated with a 30% increase in the risk of death.[17]

In most studies, factors such as sex, race, BMI at the initiation of treatment, CD4 T-cell levels, HIV-1 viral load (VL), and prior acquired immunodeficiency syndrome (AIDS), were shown to be associated with weight gain in treatment-naïve PWH, in addition to the type of drugs. However, the association between weight gain and clinical presentation (early or advanced) was not specifically explored, although the initial signal came from two trials that included many people with advanced HIV disease.[3, 4] The return-to-health phenomenon could confuse the effect of treatment on weight gain.

In this context, we aimed to study the factors associated with weight gain in ART-naive PWH initiating combined antiretroviral treatment (cART) in France between 2012 and 2018 according to clinical

131 presentation (early or advanced) and each component of the treatment combination using a large
132 cohort of PWH, the ANRS CO4-French Hospital Database on HIV (FHDH) cohort.
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MATERIALS AND METHODS

Participants

The ANRS CO4 FHDH (French Hospital Database on HIV) is an ongoing open hospital cohort that collects clinical, biological, and therapeutic data of adult PWH since 1989.[18] Currently, more than 180 hospitals contribute to the data collection, 206,651 PWH have been included, and 102,030 were being followed in 2018. All participants provided written informed consent for the use of their data for research purposes. The cohort was initially approved by the French data protection authority, the CNIL (Commission Nationale de l'Informatique et des Libertés) on 27 November 1991 (Official Journal, 17 January 1992). The research authorisation was updated to comply with the new regulations, including the General Data Protection Regulation. The ANRS CO4-FHDH cohort was approved by the CEREES (Comité d'Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé) on 20 July 2018 and as a hospital data warehouse by the CNIL on 19 February 2021. The cohort received the authorisation to conduct research projects on the data warehouse by the CNIL on 30 March 2021.[19]

For the present analysis, we selected ART-naïve PWH infected with HIV-1 who initiated cART between 2012 and 2018. Participants had to have had at least one BMI measurement within six months prior to cART initiation (baseline) and one during the follow-up and to have initiated cART at least one year before the last recorded FHDH visit in the centre. We excluded transgender participants because of the interaction of hormone therapy with weight and pregnant women were censored at the time of pregnancy. Only participants with cART combinations taken by at least 140 PWH were considered.

Statistical analysis

In addition to the whole population, we choose to study two contrasting groups, PWH with early or with advanced presentation, to better assess the differential impact of treatment initiation according of HIV disease stages and with the hypothesis that the issue of return to health would be less pronounced in PWH presenting early.

PWH presenting early were defined as participants initiating cART at primary infection or with CD4 T cells >350/mm^3 and a VL <100000 copies/mL and without AIDS at cART initiation and PWH presenting with advanced HIV disease as participants with AIDS or CD4 T cells <200/mm^3 not at primary infection at cART initiation.

As primary endpoint, we considered the rates of weight gain of at least 10%, which is often considered to be clinically significant,[20] and as secondary endpoints weight change after cART initiation and BMI increase≥5kg/m^2. Rates of weight gain of at least 10% and BMI increase≥5kg/m^2 were estimated at 30 months using Kaplan Meier estimates. Follow-up was censored at treatment modification, at the last available weight measurement, or at 30 months, whichever occurred first. We assessed the factors associated with these endpoints using Cox regression models adjusted for gender-age class (women >50 years, women ≤50 years, men >50 years, men ≤50 years), transmission group (men who have sex with men (MSM) versus others), geographic origin (Sub-Saharan Africa (SSA) versus other), baseline CD4 T cells (<200, 200-350, 350-500, ≥500/mm^3), baseline VL (50-30,000, 30,000-100,000, 100,000-500,000, ≥500000 copies/mL), AIDS status (tuberculosis, AIDS-defining cancer, other AIDS diagnosis or no AIDS), and BMI category (underweight (<18.5 kg/m^2), normal weight (18.5-24.9), overweight (25-29.9), obesity (≥30)). The gender-age class categories were chosen because previous data showed that weight/fat gain was higher among women >50 years of age, probably due to their menopausal status.[21]

In the models, we separately considered the nucleoside analogue backbones (TDF/FTC, TAF/FTC, abacavir and lamivudine (ABC/3TC)) and the third antiretroviral agent (raltegravir, dolutegravir, or elvitegravir for INSTIs; darunavir or atazanavir for PIs; and efavirenz or rilpivirine for NNRTIs). A

sensitivity analysis excluding participants presenting with AIDS was conducted for the primary endpoint.

The association between weight change and time since cART initiation was assessed using a mixed linear model with a spatial power law covariance structure to account for irregular duration between clinical visits[22] and adjusted for the same variables as previously described.

All analyses were conducted overall and separately in two subgroups according to early presentation or advanced presentation, except for the factors associated with an increase in BMI of at least 5 kg/m^2. The change in BMI pattern was assessed in the two subgroups in the first 30 months (±1.5 months). All statistical analyses were conducted using SAS 9.4. A p-value ≤5% denoted statistical significance.

RESULTS

Overall, 12,773 ART-naïve PWH initiating cART between 2012 and 2018 were included, accounting for 28,737 person-years (median 1.76 years (interquartile range (IQR), 0.71-3.32)). Among them, 5,794 presented with an early HIV disease and 3,106 with an advanced HIV disease, with a median follow-up of 2.05 (IQR, 0.84-3.74) and 1.44 (IQR, 0.56-2.90) years, respectively. The median number of weight measurements was 5 (IQR 3-7), with no difference according to the clinical presentation nor the baseline category of BMI. Participants' characteristics are presented in Table 1. Overall, 75.6% of the population was men and MSM accounted for approximately half of the participants. A quarter of the population originated from SSA. At cART initiation, the median CD4 T-cell level was 377/mm^3, median VL 4.7 log copies/mL, and median BMI 23.0 kg/m^2 (IQR, 20.7-25.8). At cART initiation, 8.2% of the participants were obese and 22.2% overweight: 20.6% and 30.7% for women originating from SSA, 8.8% and 29.6% for men originating from SSA, 15.3% and 23.2% for other women, and 4.2% and 18.8% for other men, respectively.

Among the total population (Table 1), 41.7% initiated cART with a PI-based regimen, mostly with darunavir, 33.3% with an INSTI-based regimen, mostly with dolutegravir or elvitegravir, and 25.0% with a NNRTI-based regimen, mostly rilpivirine. TDF/FTC was the most frequently used backbone (78.2%), whereas only 1,989 (15.6%) PWH received ABC/3TC and 800 (6.3%) TAF/FTC. The number of participants receiving each specific cART combination is presented in Table S1.

The characteristics differed highly according to advanced or early presentation. PWH with advanced presentation were older (median 42 versus 36 years), less likely to be MSM (29.0% versus 57.1%), more likely to have originated from SAA (36.3% versus 20.3%), more likely to be underweight (12.6% versus 5.0%), and more likely to have received a PI-based regimen (56.2% versus 30.5%) and less likely an INSTI-based regimen (11.6% versus 35.7%).

Weight gain of at least 10%

At 30 months, 34.5% (95%CI 33.5-35.6) of the PWH had a weight gain of at least 10%, 20.9% (95%CI 19.6-22.2) among PWH with early presentation and 63.1% (95%CI 60.9-65.3) among those with advanced presentation (Table 2-4). Higher risks were observed for women, non-MSM, underweight PWH, and those with more profound immunodeficiency, higher VL, and prior AIDS, with no difference between AIDS-defining events. In the overall population, the percentage of PWH with a weight gain of at least 10% at 30 months ranged from 20.9% among those receiving rilpivirine to 44.3% among those receiving raltegravir. In adjusted analyses, PWH initiating cART with dolutegravir or raltegravir had a higher risk of a weight gain of at least 10% than those initiating with other drugs, except PIs, with no significant differences between them. Those initiating with efavirenz had a lower risk of a weight gain of at least 10% than with the other drugs, except rilpivirine (Table S2a). TAF/FTC was associated with a significantly higher risk of weight gain of at least 10% than TDF/FTC (HR=1.52, 95%CI 1.29-1.79) or ABC/3TC (HR=1.61, 95%CI 1.31-1.96), whereas there was no statistical difference between ABC/3TC and TDF/FTC (HR=0.95, 95%CI 0.84-1.06) (Table 2).

Among early-presenters, the percentage of weight gain of at least 10% ranged from 11% with efavirenz to 27% with ATV/RTV. In adjusted analyses, there was no statistical difference among the

various INSTIs or between PIs, or between INSTIs and PIs. Detailed results are reported in Table 3 and Table S5a. Among PWH with advanced HIV disease, the percentage of weight gain of at least 10% ranged from 37% with rilpivirine to 74% with raltegravir. Detailed results are reported in Tables 4 and Table S5b.

In the sensitivity analysis excluding participants presenting with AIDS (Table S7), the proportion of participants with a weight gain of at least 10% was 30.9% instead of 34.5% in the whole population. The results of the Cox model evaluating the factors associated with this weight gain were similar to those of the analysis of the whole sample.

Weight change overtime

The mean weight changes estimated by multivariable mixed regression models at 12, 24 and 30 months are presented in Table 5 for the total population. At 30 months, the adjusted mean weight gain was +7.9 kg (95% confidence interval [CI] 7.1-8.6). Most of the weight gain occurred in the first 12 months. ~~The weight plateaued after 24 months~~. Weight gains were significantly larger among women, PWH originating from SSA, non-MSM, underweight PWH, and those with more profound immunodeficiency, higher VL, and prior AIDS, with no difference between AIDS-defining events. The results and comparisons according to the various drugs are presented in Table S2b and Figure 1a for third agents and Figure 1b for nucleoside backbones. Over 30 months, the adjusted weight gain was the highest for PWH receiving dolutegravir (+8.7 kg) and raltegravir (+8.5 kg) and the lowest for those receiving efavirenz (+6.5 kg). Weight gain with raltegravir was significantly greater than that with efavirenz, whereas there was no statistical difference with any other third agent. Weight gain with dolutegravir was significantly greater than that with darunavir, atazanavir, rilpivirine, or efavirenz. Weight gain with TAF/TDF was greater than that with TDF/FTC ($p<0.0001$) and ABC/3TC ($p=0.05$), and weight gain with ABC/3TC was greater than that with TDF/FTC ($p=0.04$) (Figure 1b and Table S2b).

Weight gain varied highly according to whether PWH initiated cART early or at advanced HIV disease. Among early-presenters, the adjusted mean weight gain at 30 months was +2.8 kg ranging from 1.8

kg for efavirenz to 3.5 kg for dolutegravir. Detailed results are reported in Figure 1c and 1d and Table S3.

Among PWH with advanced HIV disease, the adjusted mean weight gain was +9.7 kg at 30 months, the detailed results are reported in Figure 1e and 1f and Table S4. Over 30 months, the adjusted weight gain was the highest for PWH receiving dolutegravir (+10.9 kg), raltegravir (+10.6 kg), or atazanavir (+10.2 kg) and the lowest for those receiving elvitegravir (+8.4 kg) (Figure 1e and Table S4).

BMI increase and BMI categories over time

Overall, 9.1% of participants (95%CI 8.5-9.8) had a BMI increase of at least 5 kg/m^2, 3.4% (95%CI 2.8-4.0) among those presenting early and 23.9% (95%CI 21.9-26.1) among those with advanced HIV disease. In adjusted analyses, a higher risk of a BMI increase of at least 5 kg/m^2 was observed with raltegravir than with any other drugs, except dolutegravir, and with TAF/FTC than with TDF/FTC (HR=1.68, 95%CI 1.19-2.38) or ABC/3TC than with TDF/FTC (HR=1.28, 95%CI 1.02-1.61) (Table S6a and S6b). For the other factors, the association with a BMI increase of at least 5 kg/m^2 was in the same direction as in the other analyses, except for BMI. The risk of a BMI increase of at least 5 kg/m^2 was higher for both underweight (HR=1.33, 95%CI 1.07-1.67) and obese participants (HR=1.26, 95%CI 0.98-1.61).

The pattern of BMI categories over time was stable among PWH presenting early but changed for PWH with advanced HIV disease, with more obese PWH, especially for those receiving raltegravir, dolutegravir, or atazanavir (Figures S1 and S2).

DISCUSSION

In this observational study, a small weight gain over 30 months was observed among ART-naïve PWH presenting early in the course of HIV disease, whereas it was large among those presenting with advanced HIV disease, with a mean increase of 2.8 kg and 9.7 kg, respectively. At 30 months, 34.5% of the PWH had a weight gain of at least 10% and 9.1% a BMI increase of at least 5k g/m^2. Among those presenting early, 20.9% had a weight gain of at least 10% and 3.4% a BMI increase of at least 5 kg/m^2, whereas among those presenting with advanced HIV disease, the corresponding values were 63.1% and 23.9%, respectively. The weight gain trajectories were similar for the early and advanced presenters, with most of the weight gain occurring during the first year. Concerning the drugs received, the results differed within each class and varied by outcome (a weight gain of at least 10% or weight change), making it difficult to draw any general conclusions. However, raltegravir and dolutegravir were consistently associated with higher risk of weight gain than the other third agents and TAF was also associated with higher risk of weight gain than TDF or abacavir.

Many studies have shown that lower CD4 T-cell levels, higher viral load, and a prior AIDS event are associated with weight gain among ART-naïve PWH initiating treatment.[6-8, 23] We show here that the weight gain following treatment initiation is mainly observed in PWH with presenting with advanced HIV disease, whereas the weight gain among PWH presenting early is limited. At treatment initiation, PWH presenting with advanced HIV disease had a lower BMI than those presenting early with median values of 22.3 kg/m^2 (IQR, 19.9-25.1) and 23.2 kg/m^2 (IQR, 21.2-25.7) respectively, and the proportion of participants with a weight gain of at least 10% were significantly larger among underweight PWH (58.4%) than among obese PWH (28.4%) at 30 months. The previously reported deleterious effect of HIV infection on adipose tissue morphology, function, and metabolism may be more pronounced in PWH presenting with advanced HIV disease and could explain the large weight gain observed among these individuals.[24-26] In PWH with advanced presentation, part of the weight gain may simply be a return to health, and the clinical consequences, if any, could be limited to those who become obese. However, it would be preferable not to be diagnosed late because of the

unknown consequences of rapid weight gain associated with treatment initiation and the already known long-term consequences of advanced presentation[27], which underlines the need of continued efforts to diagnose PWH early. Overall, 9.1% of PWH initiating cART had a BMI increase of at least 5 kg/m^2, known to be associated with deleterious health outcomes.[17] Interestingly, the percentage of those showing such an increase was significantly higher in both underweight (17.0%) and obese (12.4%) PWH, (hazard ratio (HR) 1.33, 95%CI 1.07-1.67 and 1.26, 95%CI 0.98-1.61, respectively relative to PWH with a BMI in the normal range) which may lead to different health consequences in these two groups.[28] Additional studies are therefore needed on obese PWH with such weight gain to assess its consequences in terms of metabolic and cardiovascular outcomes.[29]

As in the two initial clinical trials reporting weight gain, we show that, among ART-naïve PWH initiating treatment, weight gain with dolutegravir is greater than that with efavirenz.[3, 4] Since the publication of these trials, this result has been completed with studies of weight gain after initiating treatment with other third drugs, such as raltegravir, bictegravir, elvitegravir, darunavir, atazanavir, and rilpivirine. In accordance with our results, one large cohort study from northern America showed that raltegravir and dolutegravir were associated with more weight gain than elvitegravir-, NNRTI- or PI-based regimens.[6] In pooled analyses that included eight clinical trials comparing weight gain in ART-naïve PWH initiating dolutegravir, bictegravir, elvitegravir, atazanavir, and NNRTIs, the authors found that dolutegravir and bictegravir were associated with more weight gain than elvitegravir, atazanavir, or NNRTIs.[8] In another recent American cohort study, elvitegravir was associated with lower weight gain than bictegravir and dolutegravir after six months.[11] Thus, more weight gain was observed with INSTIs other than elvitegravir. Recent studies showed that dolutegravir, bictegravir, and raltegravir can directly affect adipocytes and adipose tissue.[13, 14] Although raltegravir has been consistently shown to be associated with the worst weight gain, the current practical consequences are probably limited, because it is no longer frequently used to initiate treatment. In the entire group, efavirenz was associated with less weight gain than all the other drugs, supporting the hypothesis that it could inhibit weight gain. Concerning backbone drugs, we observed a higher risk of

weight gain with TAF/FTC than TDF/FTC, regardless of the criteria used to define weight gain, similar to many published studies.[4, 7, 8, 10, 11] Of note in our study TAF/FTC, was only available in France in multidrug pills, either with rilpivirine or boosted elvitegravir. Overall, the observed effects of the various drugs were not class effects per se. In the INSTI class, elvitegravir was associated with a lower weight gain than the other INSTIs and TAF with a higher weight gain than the other NRTIs.

For clinical practice, our results suggest that it would be important to monitor weight gain in the first year after cART initiation and to carefully select the prescribed regimen, balancing its virological and immunological advantages with its consequences in terms of weight gain, in particular for PWH presenting with advanced HIV disease or who are obese.[29] Given the persisting high proportion of people diagnosed with advanced presentation, 29% in France in 2021[30], this could concern a large proportion of newly diagnosed PWH.

The main strength of our study was its large size, allowing us to study the risk of weight gain according to whether PWH presented early or with advanced HIV disease and to the type of drug. Distinguishing two subgroups of participants allowed us to reduce the confusion between the effect of the HIV infection itself and the impact of the drugs on weight gain. Studying the association of weight gain by drug rather than by the class of drug allowed us to highlight the differential effects of drugs from the same class on weight gain. Among the limits of our study, bictegravir could not be analyzed due to the study period, which preceded its availability in France. Data on physical activity and diet are not collected in the FHDH and therefore could not be accounted for. The study also lacked pre-HIV measures of weight, which could have helped to assess the return to health phenomenon, and the composition of the body changes following cART initiation.

In conclusion, weight gain was mainly observed among participants presenting with advanced HIV disease. The limited weight gain observed among PWH presenting early emphasizes, once again, the need to be diagnosed early for early immediate treatment. Multiple factors are associated with weight gain and the choice of initial treatment should depend on the characteristics of each PWH. In

further studies, it would be important to assess the population of PWH for whom clinical consequences of the observed weight gain could occur.

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AUTHORS AND CONTRIBUTION

DC, SG, JC, and VP designed the study. SA, LB, CA, FC, PT, CD, PE, CK, MAK, OL, SM, GM, HM, JLM, JP, LP, LS, SR, and PT included PWH. VP analyzed the data. SG, VP, and DC drafted the manuscript, had full access to the data, verified the data, and had final responsibility for the decision to submit the study for publication. All authors were involved in the interpretation of the data and critical revision of the manuscript and approved the final version.

TRANSPARENCY DECLARATIONS

CA received personal fees from Gilead, Janssen-Cilag, MSD, and ViiV Healthcare for travel grants and honoraria outside the submitted work. LP reports personal fees from Pfizer (2022). F Caby reports personal fees from Gilead, ViiV Healthcare, and MSD for lectures and serving on an expert board outside the submitted work. PdT received personal fees for workshop participation and travel grants

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Table 1. Individual characteristics of all PWH and according to their clinical presentation at cART initiation

	All PWH (n = 12773)		PWH presenting early (n = 5794)		PWH presenting with advanced HIV disease (n = 3106)	
	n or median	% or [IQR]	n or median	% or [IQR]	n or median	% or [IQR]
Age	38	[30-48]	36	[29-46]	42	[34-51]
Gender						
Men	9653	75.6	4481	77.3	2166	69.7
Women	3120	24.4	1313	22.7	940	30.3
Age and gender						
Women ≤ 50 years	2440	19.1	1043	18.0	723	23.3
Women > 50 years	680	5.3	270	4.7	217	7.0
Men ≤ 50 years	7831	61.3	3831	66.1	1544	49.7
Men > 50 years	1822	14.3	650	11.2	622	20.0
Transmission group						
MSM	6147	48.1	3309	57.1	900	29.0
Injecting drug users	204	1.6	74	1.3	58	1.9
Heterosexual	5777	45.2	2171	37.5	1907	61.4
Other	645	5.0	240	4.1	241	7.8
Geographic origin						
Sub-Saharan Africa	3288	25.7	1175	20.3	1127	36.3
Other	9485	74.3	4619	79.7	1979	63.7
BMI (kg/m^2)	23.0	[20.7-25.8]	23.2	[21.2-25.7]	22.3	[19.9-25.1]
Underweight (< 18.5)	917	7.2	287	5.0	391	12.6
Normal [18.5-25[	7974	62.4	3589	61.9	1925	62.0
Overweight [25-30[	2838	22.2	1368	23.6	591	19.0
Obese (≥ 30)	1044	8.2	550	9.5	199	6.4
Year of HIV-1 diagnosis	2014	[2012-2016]	2014	[2012-2016]	2014	[2012-2016]
3rd agent						
RAL	469	3.7	155	2.7	186	6.0
DTG	1922	15.0	877	15.1	460	14.8
EVG/COBI	1866	14.6	931	16.1	354	11.4
DRV/RTV	4448	34.8	1401	24.2	1522	49.0
ATV/RTV	879	6.9	364	6.3	223	7.2
EFV	854	6.7	363	6.3	188	6.1
RPV	2335	18.3	1703	29.4	173	5.6
Backbone						
TDF/FTC	9984	78.2	4417	76.2	2495	80.3
TAF/FTC	800	6.3	419	7.2	153	4.9
ABC/3TC	1989	15.6	958	16.5	458	14.7
CD4 (cells/mm^3) at cART initiation	377	[220-539]	520	[422-672]	105	[44-167]
< 200	2861	22.4	43*	0.7	2814	90.6
200-350	2911	22.8	216*	3.7	157	5.1
350-500	3178	24.9	2390	41.2	77	2.5
≥ 500	3823	29.9	3145	54.3	58	1.9

	All PWH (n = 12773)		PWH presenting early (n = 5794)		PWH presenting with advanced HIV disease (n = 3106)	
	n or median	% or [IQR]	n or median	% or [IQR]	n or median	% or [IQR]
Viral load (copies/mL) at cART initiation	4.7	[4.1-5.3]	4.3	[3.7-4.7]	5.2	[4.8-5.7]
]50-30 000]	5058	39.6	3658	63.1	484	15.6
]30 000-100 000]	3110	24.3	1708	29.5	655	21.1
]100 000-500 000]	3018	23.6	269*	4.6	1189	38.3
> 500 000	1587	12.4	159*	2.7	778	25.0
Prior AIDS defining event						
No	11665	91.3			2009	64.7
Tuberculosis	262	2.1			261	8.4
AIDS cancer	175	1.4			173	5.6
Other AIDS defining event	671	5.3			663	21.3

* Diagnosed at primary infection

Abbreviations: RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir; DRV, darunavir; ATV, atazanavir; EFV, efavirenz; RPV, rilpivirine; COBI, cobicistat; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; MSM, male who have sex with male; BMI, body-mass index

Table 2. Factors associated with a weight gain of at least 10%: univariable and multivariable Cox regression models for all PWH (n=12773)

Characteristics	N	Δ weight ≥ 10%	Univariable Cox		Multivariable Cox	
		Kaplan-Meier estimates at 30 months [95% CI]	HR [95% CI]	P	HR [95% CI]	P
Total	12773	34.5 [33.5-35.6]				
3rd agent						
RAL	469	44.3 [38.9-50.1]	2.75 [2.28-3.32]	<0.0001	1.44 [1.18-1.76]	<0.0001
DTG	1922	36.9 [34.2-39.7]	2.07 [1.81-2.36]		1.48 [1.26-1.74]	
EVG/COBI	1866	34.0 [31.3-36.9]	1.82 [1.59-2.08]		1.12 [0.96-1.30]	
DRV/RTV	4448	44.0 [42.0-46.1]	2.61 [2.33-2.92]		1.38 [1.22-1.56]	
ATV/RTV	879	38.1 [33.8-42.7]	2.01 [1.70-2.37]		1.26 [1.06-1.50]	
EFV	854	24.9 [21.6-28.6]	1.28 [1.06-1.53]		0.90 [0.74-1.08]	
RPV	2335	20.9 [19.1-22.8]	1		1	
Backbone						
TDF/FTC	9984	33.6 [32.4-34.8]	1	0.01	1	<0.0001
TAF/FTC	800	41.1 [36.9-45.6]	1.23 [1.08-1.40]		1.52 [1.29-1.79]	
ABC/3TC	1989	36.1 [33.6-38.7]	1.06 [0.97-1.17]		0.95 [0.84-1.06]	
Age and gender						
Women ≤ 50 years	2440	46.3 [43.8-48.8]	1.71 [1.57-1.86]	<0.0001	1.34 [1.21-1.48]	<0.0001
Women > 50 years	680	48.1 [43.5-52.9]	1.93 [1.68-2.21]		1.52 [1.31-1.76]	
Men ≤ 50 years	7831	29.0 [27.7-30.3]	1		1	
Men > 50 years	1822	36.1 [33.4-38.9]	1.39 [1.26-1.54]		1.10 [0.99-1.22]	
Transmission Group						
MSM	6147	25.5 [24.1-26.9]	1	<0.0001	1	<0.0001
Other	6626	42.7 [41.2-44.2]	1.95 [1.81-2.10]		1.42 [1.29-1.56]	
Geographic origin						
Sub-Saharan Africa	3288	43.5 [41.4-45.7]	1.46 [1.35-1.57]	<0.0001	1.07 [0.98-1.17]	0.13
Other	9485	31.2 [30.1-32.4]	1		1	
BMI (kg/m^2)						
Underweight (< 18.5)	917	58.4 [54.4-62.5]	2.50 [2.25-2.79]	<0.0001	1.78 [1.60-1.99]	<0.0001
Normal [18.5-25[	7974	34.1 [32.8-35.4]	1		1	
Overweight [25-30[	2838	30.5 [28.3-32.7]	0.78 [0.71-0.86]		0.73 [0.67-0.80]	
Obese (≥ 30)	1044	28.4 [25.0-32.1]	0.71 [0.61-0.82]		0.62 [0.54-0.72]	
CD4 (cells/mm^3)						
< 200	2861	64.1 [61.8-66.4]	5.19 [4.69-5.73]	<0.0001	2.46 [2.18-2.77]	<0.0001
200-350	2911	36.3 [34.1-38.7]	1.96 [1.76-2.19]		1.53 [1.36-1.72]	
350-500	3178	24.9 [23.1-26.9]	1.25 [1.11-1.41]		1.14 [1.01-1.28]	
≥ 500	3823	20.4 [18.9-22.1]	1		1	
Viral load (copies/ml)						
]50-30 000]	5058	23.7 [22.2-25.2]	1	<0.0001	1	<0.0001
]30 000-100 000]	3110	31.4 [29.4-33.5]	1.39 [1.26-1.54]		1.17 [1.05-1.30]	
]100 000-500 000]	3018	46.1 [43.7-48.5]	2.47 [2.25-2.71]		1.57 [1.41-1.74]	
> 500 000	1587	59.3 [55.9-62.7]	3.91 [3.52-4.33]		2.00 [1.78-2.25]	
Prior AIDS defining event						
No	11665	30.9 [29.8-31.9]	1	<0.0001	1	<0.0001
Tuberculosis	262	69.0 [61.8-75.9]	3.46 [2.91-4.13]		1.78 [1.47-2.15]	
AIDS cancer	175	62.6 [52.7-72.5]	2.83 [2.24-3.57]		1.65 [1.30-2.09]	
Other AIDS defining event	671	80.4 [76.4-84.2]	5.83 [5.25-6.47]		2.39 [2.12-2.68]	

Abbreviations: 95% CI, 95% confidence interval; RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir; DRV, darunavir; ATV, atazanavir; EFV, efavirenz; RPV, rilpivirine; COBI, cobicistat; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; MSM, male who have sex with male; BMI, body-mass index

Table 3. Factors associated with a weight gain of at least 10%: univariable and multivariable Cox regression models for PWH presenting early (at primary infection or with CD4 > 350/mm^3 and VL < 100 000 copies/mL, without AIDS). (N=5794)

Characteristics	N	Δ weight ≥ 10%	Univariable Cox		Multivariable Cox	
		Kaplan-Meier estimates at 30 months [95% CI]	HR [95% CI]	P	HR [95% CI]	P
Total	5794	20.9 [19.6-22.2]				
3rd agent						
RAL	155	19.6 [13.1-28.8]	1.11 [0.71-1.73]	<0.0001	1.07 [0.68-1.67]	0.0003
DTG	877	21.2 [18.0-24.9]	1.20 [0.97-1.49]		1.41 [1.04-1.90]	
EVG/COBI	931	25.3 [21.9-29.1]	1.48 [1.21-1.80]		1.19 [0.95-1.49]	
DRV/RTV	1401	24.8 [21.6-28.4]	1.49 [1.24-1.80]		1.34 [1.10-1.64]	
ATV/RTV	364	26.8 [21.1-33.7]	1.71 [1.29-2.26]		1.55 [1.16-2.07]	
EFV	363	11.4 [8.0-16.1]	0.62 [0.43-0.90]		0.62 [0.43-0.90]	
RPV	1703	17.7 [15.8-19.9]	1		1	
Backbone						
TDF/FTC	4417	19.8 [18.4-21.4]	1	<0.0001	1	0.0004
TAF/FTC	419	32.0 [26.5-38.3]	1.68 [1.35-2.10]		1.59 [1.23-2.06]	
ABC/3TC	958	20.7 [17.7-24.1]	1.00 [0.83-1.20]		0.79 [0.61-1.03]	
Age and gender						
Women ≤ 50 years	1043	30.0 [26.7-33.6]	1.74 [1.48-2.03]	<0.0001	1.49 [1.20-1.84]	0.0005
Women > 50 years	270	29.0 [22.7-36.5]	1.70 [1.28-2.26]		1.62 [1.18-2.23]	
Men ≤ 50 years	3831	18.2 [16.7-19.8]	1		1	
Men > 50 years	650	17.7 [14.4-21.7]	0.99 [0.78-1.25]		0.99 [0.78-1.26]	
Transmission Group						
MSM	3309	17.3 [15.7-19.0]	1	<0.0001	1	0.001
Other	2485	25.4 [23.4-27.6]	1.58 [1.38-1.81]		1.37 [1.13-1.66]	
Geographic origin						
Sub-Saharan Africa	1175	26.9 [23.9-30.2]	1.46 [1.26-1.70]	<0.0001	1.17 [0.98-1.41]	0.09
Other	4619	19.2 [17.8-20.7]	1		1	
BMI (kg/m^2)						
Underweight (< 18.5)	287	34.2 [27.8-41.7]	1.99 [1.55-2.56]	<0.0001	1.82 [1.41-2.35]	<0.0001
Normal [18.5-25[	3589	20.4 [18.8-22.1]	1		1	
Overweight [25-30[	1368	20.2 [17.7-23.0]	0.95 [0.80-1.12]		0.81 [0.69-0.97]	
Obese (≥ 30)	550	18.9 [15.2-23.5]	0.90 [0.71-1.15]		0.66 [0.51-0.85]	
CD4 (cells/mm^3)						
< 200*	43	43.6 [27.1-64.6]	2.62 [1.51-4.55]	<0.0001	1.38 [0.76-2.50]	0.12
200-350*	216	34.6 [26.4-44.5]	2.03 [1.50-2.76]		1.43 [1.01-2.02]	
350-500	2390	22.1 [20.1-24.3]	1.19 [1.04-1.37]		1.12 [0.97-1.29]	
≥ 500	3145	18.8 [17.2-20.6]	1		1	
Viral load (copies/ml)						
]50-30 000]	3658	19.0 [17.5-20.7]	1		1	<0.0001
]30 000-100 000]	1708	22.0 [19.6-24.6]	1.17 [1.01-1.36]		1.23 [1.06-1.43]	
]100 000-500 000]*	269	33.0 [25.5-42.1]	1.90 [1.42-2.52]	<0.0001	1.84 [1.33-2.54]	
> 500 000*	159	44.7 [32.4-59.3]	2.82 [1.98-4.01]		2.43 [1.63-3.64]	

* Diagnosed at primary infection

Abbreviations: 95% CI: 95% confidence interval; RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir; DRV, darunavir; ATV, atazanavir; EFV, efavirenz; RPV, rilpivirine; COBI, cobicistat; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; MSM, male who have sex with male; BMI, body-mass index

Table 4. Factors associated with a weight gain of at least 10%: univariable and multivariable Cox regression models for PWH presenting with advanced HIV disease (with AIDS or with CD4 < 200/mm^3, not during primary infection). (N=3106)

Characteristics	N	Δ weight ≥ 10%	Univariable Cox		Multivariable Cox	
		Kaplan-Meier estimates at 30 months [95% CI]	HR [95% CI]	P	HR (95% CI)	P
Total	3106	63.1 [60.9-65.3]				
3rd agent						
RAL	186	74.1 [65.5-81.9]	3.30 [2.34-4.67]	<0.0001	2.19 [1.53-3.14]	<0.0001
DTG	460	68.8 [63.2-74.2]	2.99 [2.19-4.10]		2.24 [1.60-3.14]	
EVG/COBI	354	55.6 [49.1-62.3]	2.15 [1.56-2.98]		1.39 [0.98-1.97]	
DRV/RTV	1522	65.6 [62.4-68.8]	2.68 [2.00-3.58]		1.96 [1.44-2.66]	
ATV/RTV	223	63.5 [54.7-72.3]	2.26 [1.60-3.21]		1.72 [1.20-2.47]	
EFV	188	62.7 [54.1-71.3]	2.49 [1.74-3.55]		1.80 [1.25-2.61]	
RPV	173	36.6 [28.7-45.8]	1		1	
Backbone						
TDF/FTC	2495	62.5 [59.9-65.0]	1	0.28	1	0.02
TAF/FTC	153	65.1 [55.1-75.0]	1.08 [0.85-1.36]		1.52 [1.12-2.05]	
ABC/3TC	458	65.6 [60.4-70.7]	1.11 [0.97-1.28]		0.98 [0.83-1.15]	
Age and gender						
Women ≤ 50 years	723	68.6 [64.2-72.9]	1.17 [1.03-1.33]	0.0001	1.19 [1.03-1.37]	0.01
Women > 50 years	217	72.0 [64.1-79.4]	1.40 [1.15-1.71]		1.28 [1.04-1.58]	
Men ≤ 50 years	1544	57.1 [53.9-60.3]	1		1	
Men > 50 years	622	66.8 [61.7-71.7]	1.30 [1.13-1.49]		1.20 [1.05-1.39]	
Transmission Group						
MSM	900	54.9 [50.8-59.2]	1	<0.0001	1	0.0001
Other	2206	66.4 [63.8-69.0]	1.32 [1.17-1.48]		1.32 [1.15-1.53]	
Geographic origin						
Sub-Saharan Africa	1127	64.6 [61.0-68.3]	0.96 [0.86-1.06]	0.40	1.03 [0.91-1.17]	0.65
Other	1979	62.1 [59.3-64.9]	1		1	
BMI (kg/m^2)						
Underweight (< 18.5)	391	81.1 [75.9-85.7]	2.10 [1.83-2.41]	<0.0001	1.79 [1.55-2.06]	<0.0001
Normal [18.5-25[	1925	63.3 [60.6-66.1]	1		1	
Overweight [25-30[	591	53.7 [48.2-59.4]	0.64 [0.55-0.74]		0.64 [0.55-0.75]	
Obese (≥ 30)	199	53.2 [44.1-62.9]	0.56 [0.44-0.72]		0.56 [0.43-0.72]	
Viral load (copies/ml)						
]50-30 000]	391	47.0 [41.5-52.9]	1	<0.0001	1	<0.0001
]30 000-100 000]	1925	52.4 [47.4-57.5]	1.19 [0.97-1.45]		1.22 [1.00-1.49]	
]100 000-500 000]	591	67.5 [64.0-71.0]	1.85 [1.55-2.21]		1.73 [1.45-2.08]	
> 500 000	199	76.0 [71.9-80.0]	2.44 [2.04-2.94]		2.03 [1.68-2.44]	
Prior AIDS defining event						
No	2009	56.5 [53.7-59.4]	1	<0.0001	1	<0.0001
Tuberculosis	261	68.7 [61.5-75.7]	1.44 [1.20-1.74]		1.31 [1.07-1.61]	
AIDS cancer	173	62.2 [52.2-72.2]	1.18 [0.93-1.50]		1.21 [0.95-1.55]	
Other AIDS pathology	663	81.2 [77.1-84.9]	2.42 [2.14-2.73]		2.05 [1.81-2.32]	

Abbreviations: 95% CI: 95% confidence interval; RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir; DRV, darunavir; ATV, atazanavir; EFV, efavirenz; RPV, rilpivirine; COBI, cobicistat; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; MSM, male who have sex with male; BMI, body-mass index

Table 5. Mean weight change at 12, 24, and 30 months for all PWH (n = 12773)

		Multivariable mixed model			
	N	**Weight change at 12 months (kg)**	**Weight gain at 24 months (kg)**	**Weight gain at 30 months (kg)**	**P**
Total	12773	5.45 (5.04-5.87)	7.84 (7.27-8.41)	7.85 (7.13-8.57)	
3rd agent					
RAL	469	6.04 (5.33-6.74)	8.69 (7.77-9.61)	8.51 (7.33-9.69)	<0.0001
DTG	1922	5.97 (5.43-6.50)	8.82 (8.10-9.55)	8.71 (7.81-9.61)	
EVG/COBI	1866	5.52 (5.04-6.01)	7.74 (7.07-8.40)	8.03 (7.20-8.86)	
DRV/RTV	4448	5.50 (5.04-5.95)	7.71 (7.08-8.33)	7.84 (7.05-8.63)	
ATV/RTV	879	5.23 (4.64-5.81)	7.33 (6.54-8.12)	7.44 (6.46-8.42)	
EFV	854	4.28 (3.69-4.86)	6.88 (6.10-7.66)	6.51 (5.56-7.47)	
RPV	2335	5.65 (5.17-6.14)	7.73 (7.08-8.37)	7.93 (7.11-8.74)	
Backbone					
TDF/FTC	9984	4.78 (4.39-5.17)	7.02 (6.47-7.57)	7.04 (6.36-7.71)	<0.0001
TAF/FTC	800	7.21 (6.53-7.88)	9.00 (8.20-9.81)	8.80 (7.79-9.82)	
ABC/3TC	1989	6.57 (5.96-7.18)	7.50 (6.80-8.20)	7.72 (6.84-8.60)	
Age and gender					
Women ≤ 50 years	2440	5.59 (5.11-6.06)	8.17 (7.53-8.80)	8.59 (7.78-9.40)	<0.0001
Women > 50 years	680	5.81 (5.21-6.42)	8.45 (7.63-9.26)	8.17 (7.17-8.55)	
Men ≤ 50 years	7831	5.00 (4.57-5.42)	7.21 (6.63-7.79)	7.12 (6.38-7.86)	
Men > 50 years	1822	5.41 (4.94-5.90)	7.55 (6.90-8.19)	7.54 (6.72-8.35)	
Transmission Group					
MSM	6147	5.11 (4.64-5.58)	7.55 (6.92-8.19)	7.63 (6.84-8.43)	<0.0001
Other	6626	5.80 (5.39-6.21)	8.13 (7.57-8.69)	8.07 (7.36-8.79)	
Geographic origin					
Sub-Saharan Africa	3288	5.63 (5.16-6.09)	8.22 (7.59-8.84)	8.21 (7.42-8.99)	<0.0001
Other	9485	5.28 (4.86-5.70)	7.47 (6.89-8.05)	7.50 (6.77-8.23)	
BMI (kg/m^2)					
Underweight (< 18.5)	917	6.69 (6.12-7.25)	8.76 (8.00-9.52)	8.50 (7.54-9.45)	<0.0001
Normal [18.5-25[	7974	5.55 (5.13-5.98)	7.99 (7.41-8.57)	8.03 (7.30-8.75)	
Overweight [25-30[	2838	5.10 (4.64-5.56)	7.62 (7.01-8.24)	7.71 (6.94-8.48)	
Obese (≥ 30)	1044	4.47 (3.94-5.01)	7.00 (6.28-7.71)	7.18 (6.30-8.06)	
CD4 (cells/mm^3)					
< 200	2861	7.37 (6.94-7.80)	9.72 (9.11-10.32)	9.84 (9.09-10.59)	<0.0001
200-350	2911	5.39 (4.92-5.87)	7.95 (7.31-8.59)	7.69 (6.89-8.50)	
350-500	3178	4.74 (4.27-5.22)	6.98 (6.34-7.62)	7.20 (6.41-8.00)	
≥ 500	3823	4.31 (3.84-4.78)	6.73 (6.09-7.37)	6.68 (5.87-7.49)	
Viral load (copies/ml)					
]50-30 000]	5058	4.39 (3.94-4.83)	6.69 (6.08-7.30)	6.39 (5.64-7.15)	<0.0001
]30 000-100 000]	3110	4.87 (4.41-5.33)	7.21 (6.59-7.83)	6.93 (6.16-7.70)	
]100 000-500 000]	3018	5.85 (5.39-6.32)	8.05 (7.42-8.69)	8.38 (7.58-9.19)	
> 500 000	1587	6.71 (6.19-7.23)	9.42 (8.70-10.14)	9.70 (8.79-10.62)	
Prior AIDS defining event					
No	11665	3.57 (3.29-3.85)	4.57 (4.21-4.93)	4.83 (4.38-5.28)	<0.0001
Tuberculosis	262	7.15 (6.30-8.00)	8.67 (7.53-9.81)	9.71 (7.99-11.43)	
AIDS cancer	175	3.90 (2.90-4.89)	8.51 (7.08-9.95)	7.90 (6.35-9.44)	
Other AIDS defining event	671	7.20 (6.63-7.78)	9.61 (8.80-10.42)	8.98 (7.95-10.01)	

Note: 95% confidence intervals are in parentheses

Abbreviations: RAL, raltegravir; DTG, dolutegravir; EVG, elvitegravir; DRV, darunavir; ATV, atazanavir; EFV, efavirenz; RPV, rilpivirine; COBI, cobicistat; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil; FTC, emtricitabine; 3TC, lamivudine; ABC, abacavir; MSM, male who have sex with male; BMI, body-mass index