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Immunological Efficacy and the Impact on Weight of Dolutegravir-Based Regimen in Antiretroviral Therapy (ART)-Naïve Patients with HIV Infection

Mingli Zhong[1], Xiang Zhang[2], Hongjing Guan[1], Chen Chen[2], Rentian Cai[2], Mingxue Qi[2], Yifan Su[2], Yingying Yang[2], Xinglian Xu[2], Cong Cheng[2], Hongxia Wei[2]

[1]Department of Infectious Disease, The School of Public Health of Nanjing Medical University, The Second Hospital of Nanjing, Nanjing, People's Republic of China; [2]Department of Infectious Disease, The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, Nanjing, People's Republic of China

Correspondence: Hongxia Wei, Department of Infectious Disease, The Second Hospital of Nanjing, Affiliated to Nanjing University of Chinese Medicine, 1-1 Zhongfu Road, Nanjing, Jiangsu, People's Republic of China, 210003, Email wghongxia@sina.com

Purpose: This study aimed to assess the immunological efficacy and the impact on weight of dolutegravir (DTG)-based antiretroviral therapy (ART) regimen in ART-naive people living with HIV (PLWH).

Methods: A prospective study was conducted on ART-naïve PLWH who treated with DTG-based or efavirenz (EFV)-based regimens in The Second Hospital of Nanjing. Based on previous studies, the sample size was 332 patients calculated by PASS software. Considering a 20% dropout rate, the expected sample size was 416 patients, which were 208 patients in the DTG and EFV groups, respectively.

Results: Among 416 enrolled participants, the median age was 30.0 years (25.0–43.0), 388 (93.3%) males. At baseline, patients in the DTG group had worse pre-treatment immune level, but with no significant difference in weight compared to the EFV group. After 12 months of follow-up, the CD4+ T-cell counts increased greater in the DTG group (P=0.036), while the CD4+/CD8+ T-cell ratio increased greater in the EFV group (P=0.014). There was no significant difference in the normalization of various immune indicators between the two groups. The weight gain of patients in the DTG group at different follow-up points was all significantly higher than that in the EFV group (P<0.05). Multivariate logistic regression analysis showed that DTG-based regimens (OR=4.524, 95% CI: 2.371–8.634, P<0.001), baseline VL ≥10^5 copies/mL (OR=2.563, 95% CI: 1.411–4.657, P=0.002), and baseline CD4+ T-cell counts <200 cells/μL (OR=2.595, 95% CI: 1.430–4.709, P=0.002) were risk factors for weight gain ≥5 kg during the 12-month follow-up period.

Conclusion: After 12 months of follow-up, the increase in CD4+ T-cell counts was higher in the DTG group than in the EFV group, but the overall immunological efficacy was similar in both groups. However, attention should be paid to patients' weight, especially in patients with high baseline viral load and low CD4+ T-cell counts who were treated with the DTG-based regimen.

Keywords: dolutegravir, immunological efficacy, weight, risk factors

Introduction

Human immunodeficiency virus (HIV) infection caused acquired immunodeficiency syndrome (AIDS), an immunodeficiency disease primarily characterized by T-cell immune dysfunction. AIDS mainly affected the human immune system, especially CD4+ T lymphocytes, leading to rapid decline in immune function and susceptibility to opportunistic infections or concurrent tumors,[1,2] which was a highly fatal infectious disease. The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that there were 39.9 million people living with HIV (PLWH) globally, 1.3 million new cases, and 630000 people died from AIDS-related diseases in 2023.[3]

In order to control the incidence and mortality of PLWH and to reduce the burden on them, China has been providing PLWH with free antiretroviral therapy (ART) drugs since 2003. Currently, the commonly used free ART drug

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combinations in China include: Tenofovir disoproxil fumarate (TDF) + Lamivudine (3TC) + Efavirenz (EFV) or Lopinavir/ritonavir (LPV/r), and zidovudine (AZT) +3TC+EFV. Among them, LPV/r was commonly used for patients who have failed first-line treatment or developed drug resistance. AZT has been recommended as an alternative regimen for ART in China, due to its adverse reactions such as anemia in patients. The combination of 3TC+TDF+EFV was still widely used for ART-naive PLWH in most regions of China. However, while this triple combination of drugs has good antiviral efficacy, the treatment side effects were increasingly evident, especially in the central nervous system.[4,5]

The emergence of integrase strand transfer inhibitor (INSTIs) has greatly improved the treatment of AIDS, especially the second-generation INSTI, Dolutegravir (DTG), which has shown revolutionary changes in ART after its approval and launch.[6] Due to its good virological and immunological efficacy, as well as high resistance barrier and convenient administration, DTG was currently recommended by multiple guidelines as one of the preferred drugs for the initial treatment to PLWH.[7–9]

Currently, research on the DTG-based regimens in western countries was more comprehensive, but most of the studies in China[10–12] focus on a single immunological recovery indicator, such as evaluating immune recovery based on the growth of CD4+ T-cell counts. Other immune indicators, such as CD4+ T-cell percentage and CD4+/CD8+ T-cell ratio, have been proven to predict the occurrence of AIDS-related or non-related events and mortality.[13–16] Still, they were rarely included in the evaluation of immune recovery. In addition, research was increasingly focusing on the impact of DTG-based regimens on weight and metabolism. It has been reported that ART-naïve or treatment-experienced PLWH who switched to DTG-based regimens experienced a higher weight gain than PLWH treated with other ART regimens.[17–19] However, different conclusions have also been drawn, and no significant association was found between ART regimens and the rate of weight gain in ART-naïve PLWH,[20] and the overall rate of weight gain did not change or show any association with DTG-based regimens in treatment-experienced PLWH.[21,22] Furthermore, a pooled analysis of risk factors for weight gain in PLWH showed a correlation between race and weight gain, which with a higher risk of weight gain in black individuals, especially black women.[23] However, there were few studies on the factors that influence weight change in China. Therefore, we conducted this study to assess the immunological efficiency of DTG-based regimens in ART-naïve PLWH, followed by an assessment of DTG-based regimens on weight impact.

Methods

Study Design and Participants

This was a single-center, prospective, and observational study. The study included ART-naïve PLWH who treated with DTG-based regimens or a commonly used ART regimen (3TC+TDF+EFV) in the Second Hospital of Nanjing from January 2021 to January 2022. The inclusion criteria of this study were as follows: (a) aged at least 18 years; (b) diagnosed with HIV/AIDS according to the Health Industry Standard of the People's Republic of China (WS293-2019) – Diagnosis of AIDS and HIV Infection; (c) no prior ART treatment; (d) received at least one dose of DTG-based therapy or 3TC+TDF+EFV therapy; (e) no pre-existing drug resistance to the medication taken; (f) established ART follow-up records at the Second Hospital of Nanjing, with complete baseline data; (g) patient informed consent. The exclusion criteria were as follows: (a) known to be allergic to the study drug; (b) patients who have used the study drug for post-exposure prophylaxis; (c) with pre-existing resistance to the medication being taken; (d) alanine transaminase (ALT) or aspartate transaminase (AST) >200U/L; (e) patients with chronic renal failure requiring dialysis.

Sample Size

In the ENCORE1 study,[24] the CD4+ T-cell count increased by 161 cells/μL (95% CI: 148–174) in 295 ART-naïve patients who received efavirenz (EFV) for 48 weeks, with a standard deviation of around 114 cells/μL. According to a meta-analysis, patients on a DTG-based regimen had an increase in CD4+ T-cell counts after 48 weeks of 83.04 cells/μL (95% CI: 35.19, 131.14) compared to those on an EFV-based regimen.[25] Based on the above studies, assuming a difference in CD4+ T cell count increase of 35.19 cells/μL between the DTG and EFV groups at 48 weeks, with a standard deviation of 114 cells/μL in both groups. When the significance level was 0.05, power was 80%, and the sample size was equal in both groups, the sample size was calculated to be 332 cases using the PASS software.

Considering a dropout rate of 20%, the expected sample size was 416, with 208 cases in the DTG group and 208 cases in the EFV group (Supplementary Material).

Data Collection

Investigate and collect baseline data of study subjects before receiving ART, including general information [age, gender, height, weight, body mass index (BMI)], immune status (CD4+ T-cell counts, CD4+ T-cell percentage, CD8+ T-cell count, CD4+/CD8+ T-cell ratio), HIV infection status (pre-treatment HIV-1 RNA viral load (VL), route of infection, time of HIV diagnosis, WHO clinical stage), co-existing conditions (syphilis, hepatitis B, and hepatitis C), biochemical indicators (Cr, eGFR, ALT, AST), and whether they were combined with other medications. In addition, pre-treatment drug resistance data of the study subjects were collected. Based on Sanger sequencing of peripheral blood samples before ART and online comparison with the Stanford HIV Drug Resistance Database (http://HIVDB.stanford.edu/), the baseline drug resistance level was classified into five categories: sensitive, potential low-level, low-level, moderate, and high-level resistance. In this study, low-level, moderate, and high-level drug resistance detected at baseline were defined as pre-treatment drug resistance, and PLWH with pre-treatment drug resistance were excluded.

Prospective follow-up and treatment data were collected at 1 month, 3 months, 6 months, and 12 months after ART initiation, including CD4+ T-cell count, CD4+ T-cell percentage, CD8+ T-cell count, CD4+/CD8+ T-cell ratio and weight. Immunological data collection was conducted at 3 months, 6 months, and 12 months after ART, as the immune status of patients was typically assessed starting from 3 months after ART initiation in clinical practice. Data collection was discontinued if treatment was interrupted, which is defined as any modification to the initial ART regimen (including substitution, addition, or discontinuation of any drugs in the initial ART regimen), or no ART prescription for more than 90 days since the last dispensing, and inability to contact the patient or death.

This study data were obtained from medical records during the treatment and follow-up of the enrolled patients, including outpatient follow-up files, laboratory test reports, and outpatient or inpatient systems medical records. Follow-up data was recorded in a timely manner, and underwent staged data verification to promptly check and correct any abnormal or incorrectly entered data.

Ethical Clearance

This study has obtained approval from the Second Hospital of Nanjing ethics committee (approval number: 2019-LS-ky007). The study was conducted in accordance with the Declaration of Helsinki.

Primary Endpoint

The primary endpoint was an absolute change in the CD4+ T-cell count from baseline after 12 months of treatment.

Secondary Endpoint and Definitions

The secondary endpoints were included (a) median duration to achieve normalization of CD4+ T-cell count after 12 months of treatment; (b) the increase in CD4+ T-cell percentage and CD4+/CD8+ T-cell ratio compared to baseline after 12 months of treatment, and the median time to achieve normalization; (c) the proportion of PLWH achieving multiple T-cell marker recovery (MTMR) after 12 months of treatment; (d) monitoring changes in weight during the follow-up period and identifying risk factors for weight gain.

Normalization of CD4+ T-cell count was defined as counts of ≥500 cells/μL; normalization of CD4+ T-cell percentage was defined as percentages of ≥29%; normalization of CD4+/CD8+ T-cell ratio was defined as ratios of ≥1.0; and MTMR was defined as meeting the criteria of CD4+ T-cell count ≥500 cells/μL, CD4+ T-cell percentage ≥29%, and CD4+/CD8+ T-cell ratio ≥1.0.

Statistical Analysis

Categorical variables were described using frequencies (percentages) and compared between groups using the χ^2 test or Fisher's exact test. Normal continuous variables were expressed as mean ± standard deviation ($\bar{x}\pm s$), and compared between groups using the *t*-test. Otherwise, they were described using median and interquartile range [M (Q_{25} - Q_{75})] and

compared between groups using the non-parametric rank-sum test. The Cox regression model was used to adjust for confounding factors related to the normalization of immune indexes. The Kaplan-Meier method and Log rank test were used to compare the time to achieve immune normalization after starting ART in patients who did not reach immune index normalization at baseline in the DTG group and EFV group. Logistic regression analysis was used to explore the factors influencing weight gain ≥5 kg in PLWH. The variables included in the univariate analysis were gender, age at ART initiation, time interval from diagnosis to ART, baseline immune index, baseline VL, WHO clinical stage, ART regimens, and baseline weight. Variables with a univariate analysis $P<0.1$ were included in the multivariate analysis (forward: LR method). Considering that some patients interrupted treatment in the early follow-up period and had only one or no weight measurement data, only patients with two or more weight measurements were included in the analysis of the factors affecting weight changes. The sample size was calculated using PASS software, and statistical analysis and graphing were performed using SPSS 24.0 and GraphPad Prism 8 software. A two-sided $P<0.05$ was considered statistically significant for differences.

Results

Baseline Characteristics

A total of 416 ART-naïve PLWH who met the study criteria were included in the study. Among these PLWH, 208 received ART based on the DTG regimen (DTG group), and 208 treated with 3TC + TDF + EFV (EFV group). Overall, the median age of the enrolled patients was 30.0 years (25.0–43.0), 388 (93.3%) males. The main route of infection was male-to-male homosexuals, accounting for 74.8% (311/416). A total of 338 (81.3%) patients had WHO clinical stage I/II. The median baseline weight was 65.5 kg (59.0–73.9), with 127 (30.5%) patients having a baseline BMI ≥24 kg/m^2. The number of patients with co-infections of syphilis, hepatitis B, and hepatitis C were 62 (14.9%), 19 (4.6%), and 6 (1.4%), respectively. A total of 281 (67.5%) patients initiated ART within 30 days after diagnosis, while the remaining (135, 32.5%) patients started ART after more than 30 days. Baseline VL ≥ 500,000 copies/mL was observed in 119 patients (28.6%). The median baseline CD4+ T-cell count was 303.0 cells/μL (164.3–439.5), the mean CD4+ T-cell percentage was 16.2 ± 8.22%, and the median CD4+/CD8+ T-cell ratio was 0.29 (0.17–0.45). At baseline, 72 patients (17.3%) were taking other medications besides to ART drugs.

Baseline demographic characteristics of the EFV group and DTG group were similar. However, compared to the EFV group, the DTG group had more patients with WHO clinical stage III/IV ($P=0.020$), higher rates of co-infection with syphilis ($P=0.001$), more patients with baseline VL ≥ 500,000 copies/mL ($P<0.001$), and more patients taking medications other than ART drugs ($P=0.038$). In addition, the DTG group had lower CD4+ T-cell count ($P=0.005$), CD4+ T-cell percentage ($P=0.003$), and CD4+/CD8+ T-cell ratio ($P=0.001$) compared to the EFV group, as shown in Table 1.

Table 1 Baseline Characteristics Between the Two Groups

	Total (n=416)	EFV-Based (n=208)	DTG-Based (n=208)	*P*
Gender, n(%)				0.117
Male	388 (93.3)	190 (91.3)	198 (95.2)	
Female	28 (6.7)	18 (8.7)	10 (4.8)	
Age (years)	30.0 (25.0–43.0)	29.0 (24.0–45.0)	30.0 (26.0–39.0)	0.898
Transmission route, n(%)				0.813
Homosexual	311 (74.8)	156 (75.0)	155 (74.5)	
Heterosexual	95 (22.8)	48 (23.1)	47 (22.6)	
Other	10 (2.4)	4 (1.9)	6 (2.9)	
WHO clinical stage, n(%)				0.020
Stage I	309 (74.3)	167 (80.3)	142 (68.3)	
Stage II	29 (7.0)	12 (5.8)	17 (8.2)	
Stage III	46 (11.1)	20 (9.6)	26 (12.5)	
Stage IV	32 (7.7)	9 (4.3)	23 (11.1)	

(*Continued*)

Table 1 (Continued).

	Total (n=416)	EFV-Based (n=208)	DTG-Based (n=208)	*P*
Body weight (kg)	65.5 (59.0–73.9)	65.0 (58.6–72.0)	68.0 (59.0–75.0)	0.053
BMI, n(%)				0.861
<18.5kg/m^2	44 (10.6)	22 (10.6)	22 (10.6)	
18.5–23.9kg/m^2	245 (58.9)	125 (60.1)	120 (57.7)	
≥24.0kg/m^2	127 (30.5)	61 (29.3)	66 (31.7)	
Co-infection with syphilis, n(%)	62 (14.9)	19 (9.1)	43 (20.7)	0.001
Co-infection with hepatitis B, n(%)	19 (4.6)	11 (5.3)	8 (3.8)	0.481
Co-infection with hepatitis C, n(%), n(%)	6 (1.4)	3 (1.4)	3 (1.4)	>0.999
Time from diagnosis to ART, days, n(%)				0.064
≤14	147 (35.3)	63 (30.3)	84 (40.4)	
14–30	134 (32.2)	76 (36.5)	58 (27.9)	
>30	135 (32.5)	69 (33.2)	66 (31.7)	
Viral load, copies/mL, n(%)				<0.001
<10^5	297 (71.4)	165 (79.3)	132 (63.5)	
≥10^5	119 (28.6)	43 (20.7)	76 (36.5)	
CD4+ T-cell count, cells/μL	303.0 (164.3–439.5)	326.5 (216.0–448.5)	273.5 (106.5–434.8)	0.005
CD4+ T-cell percentage, %	16.2 ± 8.22	17.3 ± 7.59	15.0 ± 8.67	0.003
CD4+/CD8+ T-cell ratio	0.29 (0.17–0.45)	0.32 (0.20–0.46)	0.27 (0.13–0.41)	0.001
Combined with other medications, n(%)	72 (17.3)	28 (13.5)	44 (21.2)	0.038

Abbreviations: EFV, efavirenz; DTG, dolutegravir; BMI, body mass index; ART, antiretroviral therapy.

Immunological Efficacy

The 12-month CD4+ T-cell count in the DTG group was 455.0 cells/μL (299.5–663.5), and in the EFV group was 497.5 cells/μL (328.8–683.8), both showing significant increases compared to baseline (all $P<0.001$). However, the median difference in CD4+ T-cell count from baseline was higher in the DTG group than in the EFV group (195 cells/μL vs 158 cells/μL, $P=0.036$), as shown in (Figure 1A). The median time to achieve normalization of CD4+ T-cell counts in the DTG and EFV groups during the 12-month follow-up was 386.0 days (338.5–433.5) and 390.0 days (351.6–428.4), respectively. There was no significant difference in the median time to normalization between the two groups ($P=0.915$), as shown in (Figure 2A).

The median difference in CD4+ T-cell percentage compared to baseline gradually increased during the follow-up period in both the DTG group and the EFV group, but there was no statistically significant difference between the two groups at each follow-up points ($P > 0.05$), Figure 1B). Similarly, the median difference in CD4+/CD8+ T-cell ratio compared to baseline also showed an increasing trend, which the median increase of CD4+/CD8+ T-cell ratio at 12 months of follow-up in the EFV group was significantly higher than that in the DTG group (0.26 > 0.21, $P=0.014$), Figure 1D). In addition, the median difference level of CD8+ T-cell count compared to baseline in the DTG group was higher than that in the EFV group at each follow-up point after ART ($P < 0.05$), and the median difference compared to baseline at 3 and 6 months of follow-up in the DTG group were 80 cells/μL and 74 cells/μL, respectively. This indicated that the DTG-based regimen not only promoted an increase of CD4+ T-cell count in the early stages of ART, but also led to an increase in the CD8+ T-cell count, Figure 1C).

There was no significant difference in the median time to achieve normalization of the CD4+ T-cell percentage at 12 months between the DTG group and EFV group [386.0 days (338.5–433.5) vs 390.0 days (351.6–428.4), $P=0.603$], as shown in Figure 2B). The median time to achieve normalization of the CD4+/CD8+ T-cell ratio was 471 days (436.4–505.6) in the EFV group, while it could not be determined in the DTG group due to insufficient follow-up time. There was no significant difference in the median time to achieve normalization of CD4+/CD8+ T-cell ratio between the two groups ($P=0.307$), Figure 2C). Furthermore, there was no significant difference ($P=0.694$) in the median time to achieve MTMR at 12 months between the DTG group and EFV group, Figure 2D).

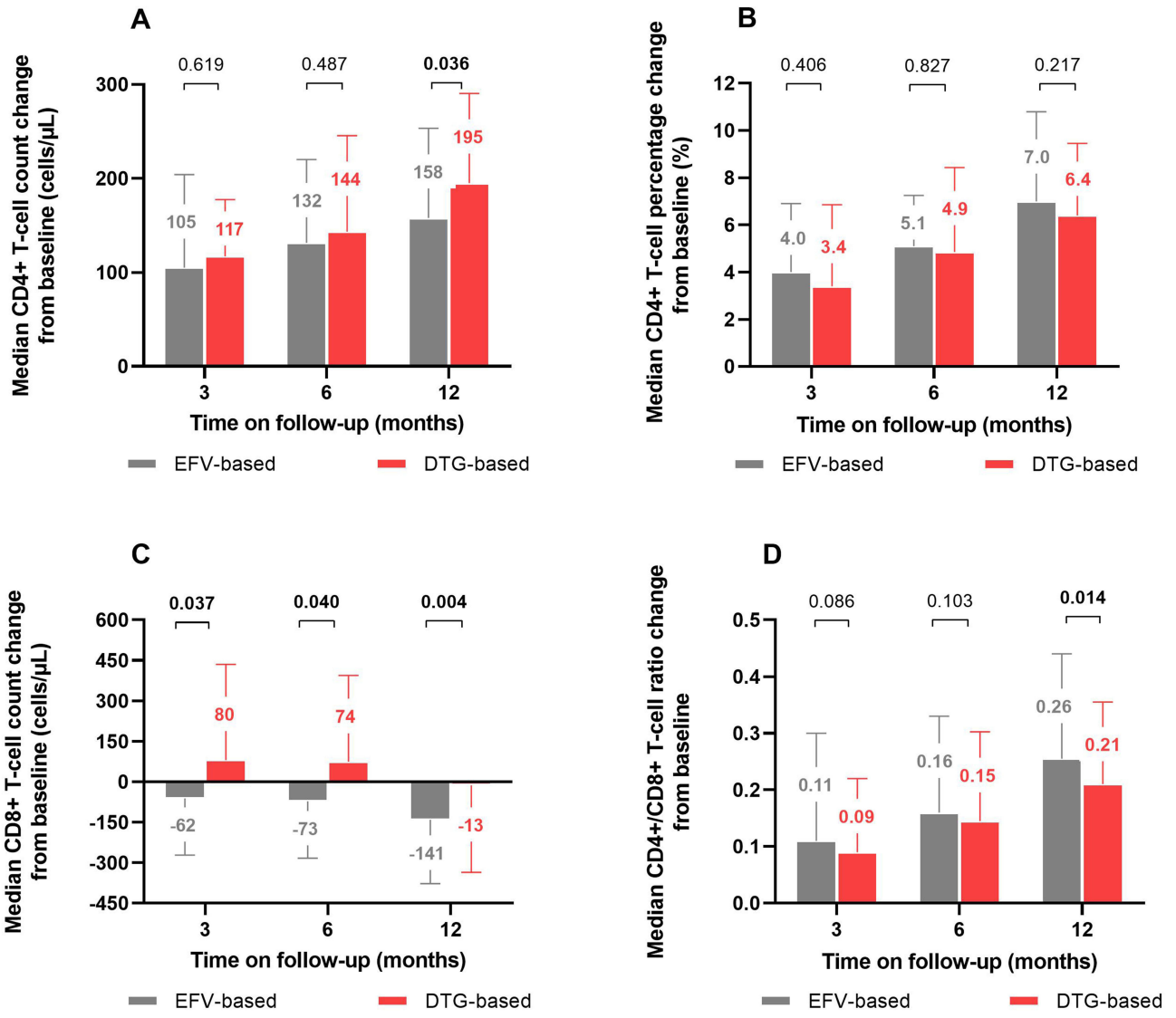

Figure 1 Median changes in immune markers between baseline and different follow-up points between the DTG group and the EFV group. (**A**) Median change in CD4+ T-cell count; (**B**) Median change in CD8+ T-cell count; (**C**) Median change in CD4+ T-cell percentage; (**D**) Median change in CD4+/CD8+ T-cell ratio.

Different ART Regimens on Immunological Normalization

After adjusting for baseline confounding factors using COX regression analysis, there were no significant difference in the impact of the DTG-based and EFV-based ART regimens on the normalization of immunological indicators, including CD4+ T-cell count ≥500 cells/μL (HR=1.340, 95% CI: 0.932–1.927, *P*=0.114), CD4+ T-cell percentage ≥29% (HR=1.462, 95% CI: 0.930–2.298, *P*=0.099), CD4+/CD8+ T-cell ratio ≥1.0 (HR=1.217, 95% CI: 0.643–2.305, *P*=0.546), and MTMR (HR=1.220, 95% CI: 0.619–2.405, *P*=0.566), Table 2.

Weight

The baseline weights of PLWH in the DTG and EFV groups were 68.0 kg (59.0–75.0) and 65.0 kg (58.6–72.0), respectively. There was no statistically significant difference in baseline weight between the two groups (*P*=0.053). However, the weight of the patients in the DTG group was significantly higher than that of the EFV group at 1, 3, 6, and 12 months after follow-up (all *P*<0.05). In particular, the weight of the DTG group was higher than that of the EFV group (70 kg (63.0–80.0) >65.0 kg (59.5–72.5), *P*<0.001) at 12 months, Figure 3. During the follow-up period, a total of 375 patients had weight measurements taken two or more times, of which 75 (20%) had a weight gain of ≥5 kg during the 12-month follow-up.

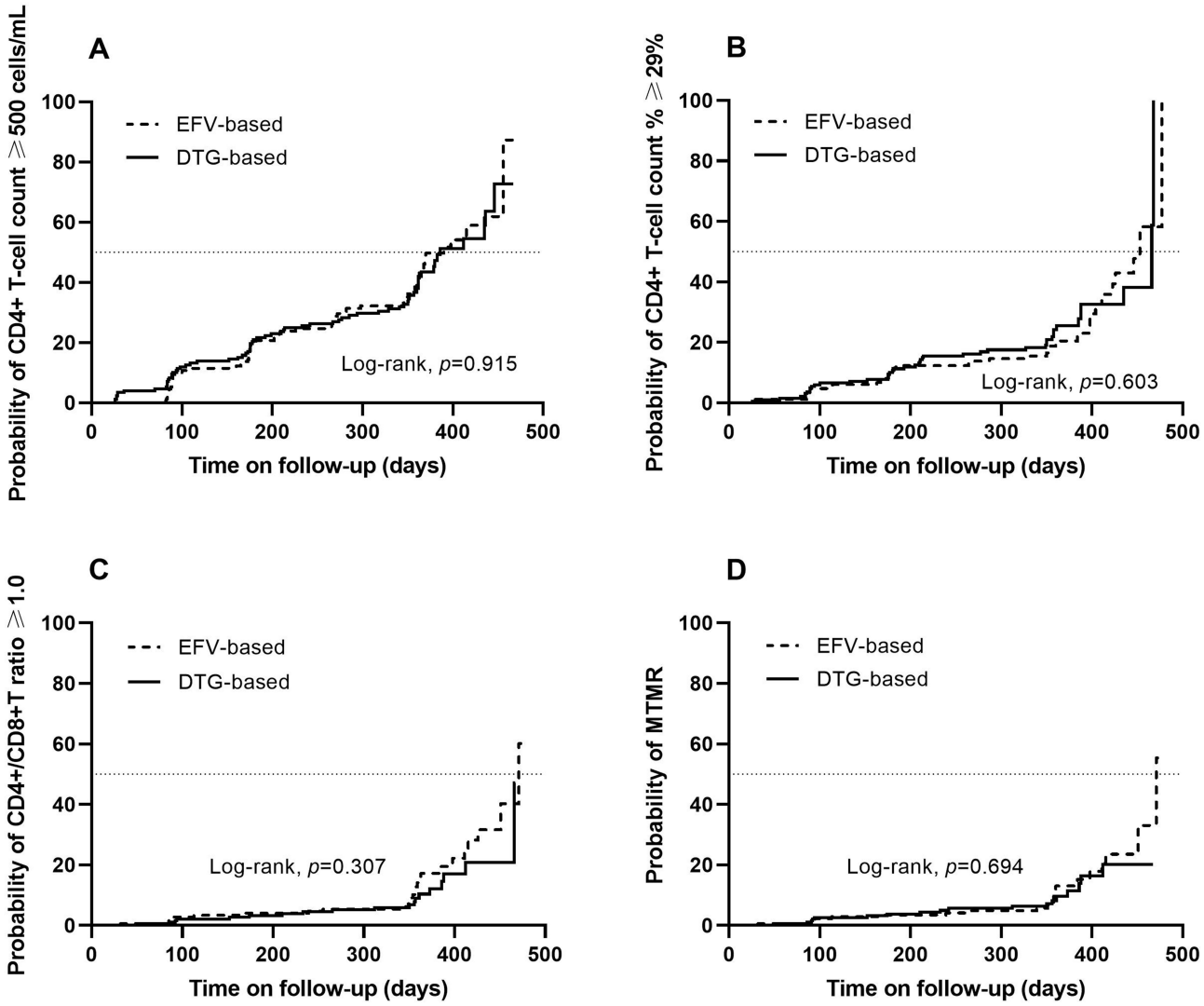

Figure 2 Kaplan-Meier plots of immunological normalization during follow-up in the DTG and the EFV groups. (**A**) Normalization of CD4+ T-cell count; (**B**) Normalization of CD4+ T-cell percentage; (**C**) Normalization of CD4+/CD8+ T-cell ratio; (**D**) Normalization of MTMR.
Abbreviations: MTMR, multiple T-cell marker recovery.

The variables of WHO clinical stage, co-infection with syphilis, duration from diagnosis to ART, baseline VL, CD4+ T-cell count, percentage of CD4+ T-cell, combined with other medications, and ART regimen were included in the multivariate analysis after univariate logistic regression analysis. Multivariate Logistic regression (FSTEP(LR)) showed that DTG-based ART (OR=4.524, 95% CI: 2.371–8.634, $P<0.001$), baseline VL $\geq 10^5$ copies/mL (OR=2.563, 95% CI:

Table 2 The Impact of DTG- and EFV-Based Regimens on the Normalization of Immunological Indicators

		Not Adjusted		Adjust for Confounders	
Normalization of the CD4+ T cell Counts		**cHR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CD4+ T-cell count ≥ 500 cells/μL	EFV-based	1.000		1.000	
	DTG-based	0.982 (0.696–1.384)	0.915	1.340 (0.932–1.927)	0.114
Normalization of the percentage of CD4+ T cells		**cHR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CD4+ T-cell percentage ≥ 29%	EFV-based	1.000		1.000	
	DTG-based	1.124 (0.723–1.749)	0.604	1.462 (0.930–2.298)	0.099

(*Continued*)

Table 2 (Continued).

		Not Adjusted		Adjust for Confounders	
Normalization of the CD4+ T cell Counts		**cHR (95% CI)**	***P***	**aHR (95% CI)**	***P***
Normalization of the CD4+/CD8+ T-cell ratio		**cHR (95% CI)**	***P***	**aHR (95% CI)**	***P***
CD4+/CD8+ T-cell ratio ≥ 1.0	EFV-based DTG-based	1.000 0.733 (0.403–1.333)	 0.309	1.000 1.217 (0.643–2.305)	 0.546
Normalization of MTMR		**cHR (95% CI)**	***P***	**aHR(95% CI)**	***P***
EFV-based DTG-based		1.000 0.880 (0.465–1.666)	 0.695	1.000 1.220 (0.619–2.405)	 0.566

Notes: Multivariable Cox regression adjusted for baseline CD4+ T-cell count, CD4+ T-cell percentage, CD4+/CD8+ T cell ratio, HIV viral load, WHO clinical stage, hepatitis B, syphilis infection status, time from diagnosis to ART, gender, and age to obtain aHR.
Abbreviations: cHR, crude hazard ratios; aHR, adjusted hazard ratios; EFV, efavirenz; DTG, dolutegravir; MTMR, multiple T-cell marker recovery.

1.411–4.657, *P*=0.002), and baseline CD4+ T-cell count <200 cells/μL (OR=2.595, 95% CI: 1.430–4.709, *P*=0.002) were risk factors for weight gain ≥5 kg during the 12-month follow-up period, Table 3.

Discussion

DTG was the first second-generation INSTI with good virological, immunological efficacy, high resistance barrier, and convenient dosing. It has been recommended as one of the preferred drugs for PLWH by multiple guidelines.[7–9] However, due to the high early price of DTG and other reasons, there were limited studies on DTG-based ART regimens in China, with relatively single evaluation of immunological indicators and few studies on the impact of DTG on weight. This study prospectively collected treatment follow-up data from ART-naïve PLWH who were on a DTG-based regimen for 12 months and compared it with the 3TC+TDF+EFV regimen at the Second Hospital of Nanjing, and comprehensively exploring the immunological efficacy of DTG and its impact on weight in ART-naïve PLWH, providing a reasonable reference for the clinical treatment of HIV-1 patients.

Due to the real-world study design, our participants were not randomized, resulting in incomplete baseline immune status balance between the two groups. Therefore, the study evaluated immune function not only through the detection values of immune indicators after 12 months of treatment, but also through the median change in detection values compared to baseline, and the proportion of patients achieving normalization of immune indicators to assess the

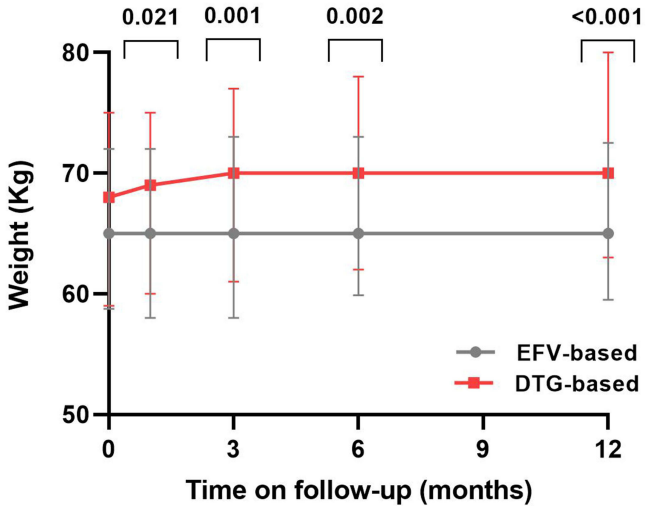

Figure 3 Changes in weight of the DTG-based and the EFV-based regimens during the follow-up period.

Table 3 Logistic Regression Analysis for Weight Gain ≥5kg During the Follow-Up Period

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender				
Male	1.000			
Female	0.479 (0.140–1.636)	0.240		
Age, per 1 year increased	1.003 (0.985–1.021)	0.754		
WHO clinical stage				
Stage I/ II	1.000			
Stage III/ IV	2.573 (1.432–4.623)	0.002		
Weight, per 10 kg increased	1.010 (0.815–1.250)	0.930		
BMI, kg/m^2				
<18.5	1.000			
18.5–23.9	1.581 (0.625–3.995)	0.333		
≥24.0	1.155 (0.430–3.105)	0.775		
Co-infection with syphilis	2.143 (1.158–3.968)	0.015		
Time from diagnosis to ART, days				
≤14	1.000			
14–30	0.594 (0.323–1.091)	0.093		
>30	0.532 (0.285–0.993)	0.047		
Viral load, copies/mL				
<10^5	1.000		1.000	
≥10^5	4.182 (2.465–7.095)	<0.001	2.563 (1.411–4.657)	0.002
CD4+ T-cell count, cells/μL				
<200	4.179 (2.464–7.086)	<0.001	2.595 (1.430–4.709)	0.002
≥200	1.000		1.000	
CD4+ T-cell percentage, per 10% increased	0.411 (0.285–0.593)	<0.001		
CD4+/CD8+ Tcell ratio, per 0.5 year increased	0.611 (0.331–1.127)	0.115		
Combined with other medications	2. 973 (1.654–5.344)	<0.001		
ART regimens				
EFV-based	1.000		1.000	
DTG-based	5.545 (2.971–10.350)	<0.001	4.524 (2.371–8.634)	<0.001

Notes: Hepatitis B and C were not included in the regression analysis, considering that less than 5% of the patients were co-infected with hepatitis B and C.

Abbreviations: OR, Odds Ratio; CI, confidence interval; BMI, body mass index; ART, antiretroviral therapy; EFV, efavirenz; DTG, dolutegravir.

immunological efficacy of the DTG-based and EFV-based regimens. The study found that after 12 months of ART, both the DTG and EFV groups showed significant increases in CD4+ T-cell counts, CD4+ T-cell percentages, and CD4+/CD8 + T-cell ratios compared to baseline, indicating that both regimens were effective in immune recovery.

However, the DTG group had a greater increase in CD4+ T-cell count than the EFV group, while the increase in the CD4+/CD8+ T-cell ratio was lower than that of the EFV group. The benefits of DTG in increasing CD4+ T-cell count have been confirmed by multiple clinical trials and observational studies, but most of these studies did not focus on changes in CD4+/CD8+ T cell ratio,[10,26–28] or only the absolute value of CD4+ T-cell count was used to define immune recovery.[29,30] A study on the use of EFV-based or DTG- regimens in acute HIV-1 patients[31] showed that the DTG group had significantly higher increases in CD4+ T-cell count and CD8+ T-cell count compared to the EFV group at 96 weeks of ART, which was consistent with the results of this study. However, it found no differences between the two groups in terms of CD4+/CD8+ T-cell ratio. Yusnelkis MG[32] also found that there was no intergroup difference in the increase of CD4+/CD8+ T-cell ratio after treatment with different ART regimens. In this study, the increase of CD4+/CD8+ T-cell ratio in the DTG group was not as significant as that in the EFV group. On the one hand, the baseline immune status of the DTG group was worse than that of the EFV group. On the other hand, the CD8+ T-cell count in the EFV group

consistently decreased after ART, while increased in the DTG group at the first 6 months after ART and started to decrease compared to baseline only after 12 months of ART, resulting in a smaller decrease compared to the EFV group and thus a smaller increase in CD4+/CD8+ T-cell ratio after 12 months.

With the prolongation of ART time, the proportion of both groups achieving normalization of immune indicators gradually increased, including CD4+ T-cell count ≥500 cells/μL, CD4+ T-cell percentage ≥29%, CD4+/CD8+ T-cell ratio ≥1.0, and achieving MTMR. However, there was no significant difference in the median time to achieve immune indicator normalization between the two groups at the 12-month follow-up. Univariate COX regression analysis showed no significant effect of the different regimens on immune indicator normalization. The difference between the two groups remained non-significant after adjusting for baseline confounding factors by multivariable Cox regression analysis. However, this study only followed up for 12 months, and a larger and longer follow-up cohort is needed to verify the long-term effects of different ART regimens on immune recovery. In addition, the recovery of a single CD4+ T-cell count did not fully reflect the normalization of T-cell homeostasis, while MTMR considered the recovery of CD4+ T-cell count, CD4+ T-cell percentage, and CD4+/CD8+ T-cell ratio, which might be a powerful predictor of immune recovery.[33] There was limited evaluation of MTMR, its clinical significance need further exploration.

In the early stages of HIV epidemic, weight gain after ART was usually considered a phenomenon of "health recovery", especially for those in advanced AIDS stage who were severely wasted.[34] However, as the survival time of PLWH increased, more and more patients became overweight or obese after starting ART,[35–37] which increased the risk of metabolic and cardiovascular diseases.[38,39] Studies have shown that different ART regimens have different effects on obesity, and regimens based on INSTIs were risk factors for weight gain after ART compared to non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[40] Multiple studies have explored the effect of DTG on weight. In two large randomized clinical trials conducted in sub-Saharan Africa, PLWH taking DTG-based regimens had a significant increase in weight compared to those taking EFV-based regimens.[41,42] PLWH, who switched from EFV-based regimens to DTG-based regimens, not only had a greater average weight gain but also had a higher risk of developing hypertension than those who continued EFV-based regimens in a recent study.[43] However, without evidence of an association between ART regimens and the rate of weight gain was found in an adjusted model.[20] Another study also showed that weight gain in PLWH was mainly influenced by pre-switch weight and low physical activity, rather than INSTIs themselves.[44] This study showed that the weight of patients in the DTG group was significantly higher than that in the EFV group at different follow-up points after ART; it was found that the DTG-based ART regimen remained a risk factor for weight gain ≥5kg after adjusting for other baseline factors through multivariate logistic regression. The results supported the view that PLWH who treated with DTG-based regimens experienced more weight gain. In addition, there might be other common factors that were associated with weight gain after taking DTG, such as race, gender, pre-treatment VL, and CD4+ T-cell count, etc.[18,23,45] In this study, baseline VL ≥10^5 copies/mL and CD4+ T-cell count <200 cells/μL were also risk factors for weight gain in patients, indicating that late-stage AIDS patients may enter a state of "health recovery" faster after starting ART. However, this study did not collect data on the difference in physical activity between the two groups of PLWH, so the association between weight gain and physical activity could not be explored.

The potential mechanisms underlying weight gain are currently unclear. The possible mechanisms include inflammation, adipocyte dysfunction, and decreased insulin sensitivity. It has been reported that there was a complex relationship between inflammation and obesity, with higher levels of inflammation in obese patients than those with normal weight.[46,47] Although most inflammatory biomarkers decreased in PLWH after starting ART, DTG might increase the expression and release of interleukin-6,[48] and might also promote the inflammatory activity of neutrophils,[49] leading to changes in patient weight. Analysis of macrophages in mice showed that DTG could increase the expression of fatty acid β-oxidation enzyme acyl-CoA hydratase short chain 1, thereby affecting macrophage lipid metabolism.[50] At the same time, DTG significantly reduced markers of brown fat formation, especially uncoupling protein 1 in brown and beige adipocytes, which leaded to decreased mitochondrial function, impaired thermogenesis, and inhibited energy expenditure, resulting in weight gain.[51] In addition, DTG and RAL might also induce adipogenesis, oxidative stress, fibrosis, and insulin resistance in human/monkey adipose tissue.[52] In the lifelong ART process of PLWH, it was necessary to clarify the long-term effects of different ART regimens on weight and the underlying mechanisms.

There were some limitations in this study. Firstly, it was an observational study and the study participants were not randomized, which might introduce unknown or uncontrolled confounding biases. Secondly, the study only had a 12-month follow-up period, so the immunological efficacy and changes in patient's weight during the long-term ART were not known. Additionally, the study only collected information on concomitant medication use at baseline and did not further collect and analyze concomitant medication used during the follow-up period, which might have affected the study results. For example, some PLWH might have taken weight loss drugs during the follow-up period, which could affect the assessment of the impact of the drug on the patient's body weight.

Conclusion

The increase in CD4+ T-cell count in the DTG group after 12 months of follow-up was higher than that in the EFV group. Both groups showed an upward trend in CD4+ T-cell percentage and CD4+/CD8+ T-cell ratio, but the DTG group also showed an increase in the early CD8+ T-cell count. During the follow-up period, the DTG group had higher weight than the EFV group. After adjusting for confounding factors, the DTG-based regimen, high baseline VL, and low CD4+ T-cell count were identified as risk factors for weight gain ≥5kg during the 12-month follow-up period.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there are no conflicts of interest in this work.

References

1. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV*. 2017;4(11):e495–e504. doi:10.1016/S2352-3018(17)30125-X
2. Dubrow R, Silverberg MJ, Park LS, Crothers K, Justice AC. HIV infection, aging, and immune function: implications for cancer risk and prevention. *Curr Opin Oncol*. 2012;24(5):506–516. doi:10.1097/CCO.0b013e328355e131
3. UNAIDS. Global HIV & AIDS statistics — fact sheet[EB/OL]; Available from: https://www.unaids.org/en/resources/fact-sheet. Accessed October 11, 2024.
4. Dai L, Su B, Liu A, et al. Adverse events in Chinese human immunodeficiency virus (HIV) patients receiving first line antiretroviral therapy. *BMC Infect Dis*. 2020;20(1):158. doi:10.1186/s12879-020-4878-2
5. Avihingsanon A, Maek ANW, Gatechompol S, et al. Efficacy and safety of a once-daily single-tablet regimen of tenofovir, lamivudine, and efavirenz assessed at 144 weeks among antiretroviral-naïve and experienced HIV-1-infected Thai adults. *Internat J Infecti Dis*. 2017;61:89–96. doi:10.1016/j.ijid.2017.06.009
6. Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. *Clin Infect Dis*. 2014;59(2):265–271. doi:10.1093/cid/ciu221
7. Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of hiv infection in adults: 2022 recommendations of the international antiviral society-USA panel. *JAMA*. 2023;329(1):63–84. doi:10.1001/jama.2022.22246
8. European AIDS Clinical Society. EACS guidelines version 11.1 (October 2022); 2022.
9. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services. Available from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. Accessed October 23, 2024.

10. Tongtong Y, Shenghua H, Yin W, et al. Effectiveness and safety of dolutegravir versus efavirenz-based antiviral regimen in people living with HIV-1 in Sichuan Province of China: a real-world study. *J Acquired Immune Deficien Syndrom*. 2022;91(S1):S1–s7. doi:10.1097/QAI.0000000000003041
11. Chen GJ, Sun HY, Chang SY, et al. Effectiveness of switching from protease inhibitors to dolutegravir in combination with nucleoside reverse transcriptase inhibitors as maintenance antiretroviral therapy among HIV-positive patients. *Int J Antimicrob Agents*. 2019;54(1):35–42. doi:10.1016/j.ijantimicag.2019.03.016
12. Li D, Xiao R, Fu Q, et al. A preliminary study on plasma concentration, short-term efficacy, and safety profile of dolutegravir in Chinese people with HIV. *Expert Rev Clin Pharmacol*. 2024;2024:1–7.
13. Guiguet M, Kendjo E, Carcelain G, et al. CD4+ T-cell percentage is an independent predictor of clinical progression in AIDS-free antiretroviral-naive patients with CD4+ T-cell counts >200 cells/mm3. *Antiviral Ther*. 2009;14(3):451–457. doi:10.1177/135965350901400311
14. Castilho JL, Shepherd BE, Koethe J, et al. CD4+/CD8+ ratio, age, and risk of serious noncommunicable diseases in HIV-infected adults on antiretroviral therapy. *AIDS*. 2016;30(6):899–908. doi:10.1097/QAD.0000000000001005
15. Hema MN, Ferry T, Dupon M, et al. Low CD4/CD8 ratio is associated with non aids-defining cancers in patients on antiretroviral therapy: ANRS CO8 (Aproco/Copilote) prospective cohort study. *PLoS One*. 2016;11(8):e0161594. doi:10.1371/journal.pone.0161594
16. Fogli M, Iaria M, Focá E, et al. For timing of HAART is less more? CD4+/CD8+ ratio and CD4+ percentage as surrogate markers for more complex immunological features. *New Microbiolog*. 2014;37(1):75–80.
17. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment-naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis*. 2020;70(7):1267–1274. doi:10.1093/cid/ciz407
18. Lake JE, Wu K, Bares SH, et al. Risk factors for weight gain following switch to integrase inhibitor-based antiretroviral therapy. *Clin Infect Dis*. 2020;71(9):e471–e477. doi:10.1093/cid/ciaa177
19. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquired Immune Deficien Syndrom*. 2017;76(5):527–531. doi:10.1097/QAI.0000000000001525
20. Burns JE, Stirrup O, Waters L, Dunn D, Gilson R, Pett SL. No overall impact on rate of weight gain with integrase inhibitor-containing regimens in antiretroviral-naïve adults. *HIV Medicine*. 2022;23(3):294–300. doi:10.1111/hiv.13186
21. Burns JE, Stirrup OT, Dunn D, et al. No overall change in the rate of weight gain after switching to an integrase-inhibitor in virologically suppressed adults with HIV. *AIDS*. 2020;34(1):109–114. doi:10.1097/QAD.0000000000002379
22. Guaraldi G, Calza S, Milic J, et al. Dolutegravir is not associated with weight gain in antiretroviral therapy experienced geriatric patients living with HIV. *AIDS*. 2021;35(6):939–945. doi:10.1097/QAD.0000000000002853
23. Sax PE, Erlandson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. *Clin Infect Dis*. 2020;71(6):1379–1389. doi:10.1093/cid/ciz999
24. Group ES. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2014;383(9927):1474–1482. doi:10.1016/S0140-6736(13)62187-X
25. Zhang K, Zhang Y, Liu X, et al. Three-drug regimens containing integrase inhibitor show good efficacy and safety in treatment-naive patients with HIV-1: a bayesian analysis. *Front Pharmacol*. 2021;12:603068. doi:10.3389/fphar.2021.603068
26. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus Abacavir-lamivudine for the treatment of HIV-1 infection. *New Engl J Med*. 2013;369(19):1807–1818. doi:10.1056/NEJMoa1215541
27. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381(9868):735–743. doi:10.1016/S0140-6736(12)61853-4
28. Hongo H, Nagao T, Nakamura K, et al. Safety and effectiveness analysis of dolutegravir in patients with HIV-1: interim report of post-marketing surveillance in Japan. *Advan Therapy*. 2021;38(8):4480–4504. doi:10.1007/s12325-021-01842-3
29. Zhong M, Li M, Qi M, et al. A retrospective clinical study of dolutegravir- versus efavirenz-based regimen in treatment-naïve patients with advanced HIV infection in Nanjing, China. *Front Immunol*. 2022;13:1033098. doi:10.3389/fimmu.2022.1033098
30. Rodríguez-Gallego E, Gómez J, Pacheco YM, et al. A baseline metabolomic signature is associated with immunological CD4+ T-cell recovery after 36 months of antiretroviral therapy in HIV-infected patients. *AIDS*. 2018;32(5):565–573. doi:10.1097/QAD.0000000000001730
31. Chan P, Yoon B, Colby D, et al. Immunological, cognitive, and psychiatric outcomes after initiating efavirenz- and dolutegravir-based antiretroviral therapy during acute human immunodeficiency virus infection. *Clin Infect Dis*. 2023;76(3):e718–e726. doi:10.1093/cid/ciac466
32. Milanés-Guisado Y, Gutiérrez-Valencia A, Muñoz-Pichardo JM, et al. Is immune recovery different depending on the use of integrase strand transfer inhibitor-, non-nucleoside reverse transcriptase- or boosted protease inhibitor-based regimens in antiretroviral-naive HIV-infected patients? *J Antimicrob Chemother*. 2020;75(1):200–207. doi:10.1093/jac/dkz421
33. Torti C, Prosperi M, Motta D, et al. Factors influencing the normalization of CD4+ T-cell count, percentage and CD4+/CD8+ T-cell ratio in HIV-infected patients on long-term suppressive antiretroviral therapy. *Clin Microbiol Infect*. 2012;18(5):449–458. doi:10.1111/j.1469-0691.2011.03650.x
34. Sudfeld CR, Isanaka S, Mugusi FM, et al. Weight change at 1 mo of antiretroviral therapy and its association with subsequent mortality, morbidity, and CD4 T cell reconstitution in a Tanzanian HIV-infected adult cohort. *Am J Clin Nutrit*. 2013;97(6):1278–1287. doi:10.3945/ajcn.112.053728
35. Koethe JR, Jenkins CA, Lau B, et al. Rising obesity prevalence and weight gain among adults starting antiretroviral therapy in the United States and Canada. *AIDS Res Hum Retroviruses*. 2016;32(1):50–58. doi:10.1089/aid.2015.0147
36. Bourgi K, Ofner S, Musick B, et al. weight gain among treatment-naïve persons with HIV receiving dolutegravir in Kenya. *J Acquired Immune Deficien Syndrom*. 2022;91(5):490–496. doi:10.1097/QAI.0000000000003087
37. Coelho LE, Jenkins CA, Shepherd BE, et al. Weight gain post-ART in HIV+ Latinos/as differs in the USA, Haiti, and Latin America. *Lancet Reg Health Am*. 2022;2022:8.
38. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol*. 2018;9:705. doi:10.3389/fendo.2018.00705
39. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173(8):614–622. doi:10.1001/jamainternmed.2013.3728
40. Bakal DR, Coelho LE, Luz PM, et al. Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors. *J Antimicrob Chemother*. 2018;73(8):2177–2185. doi:10.1093/jac/dky145

41. Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, Phase 3 non-inferiority trial in Cameroon. *Lancet HIV*. 2020;7(10):e677–e687. doi:10.1016/S2352-3018(20)30238-1
42. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7(10):e666–e676. doi:10.1016/S2352-3018(20)30241-1
43. Brennan AT, Nattey C, Kileel EM, et al. Change in body weight and risk of hypertension after switching from efavirenz to dolutegravir in adults living with HIV: evidence from routine care in Johannesburg, South Africa. *EClinicalMedicine*. 2023;57:101836. doi:10.1016/j.eclinm.2023.101836
44. Guaraldi G, Milic J, Bacchi E, et al. Contribution of integrase inhibitor use, body mass index, physical activity and caloric intake to weight gain in people living with HIV. *HIV Res Clin Pract*. 2022;24(1):1–6.
45. Taramasso L, Bonfanti P, Ricci E, et al. Factors associated with weight gain in people treated with dolutegravir. *Open Forum Infect Diseases*. 2020;7(6):ofaa195. doi:10.1093/ofid/ofaa195
46. Mave V, Erlandson KM, Gupte N, et al. Inflammation and change in body weight with antiretroviral therapy initiation in a multinational Cohort of HIV-infected adults. *J Infect Dis*. 2016;214(1):65–72. doi:10.1093/infdis/jiw096
47. Conley LJ, Bush TJ, Rupert AW, et al. Obesity is associated with greater inflammation and monocyte activation among HIV-infected adults receiving antiretroviral therapy. *AIDS*. 2015;29(16):2201–2207. doi:10.1097/QAD.0000000000000817
48. Domingo P, Quesada-López T, Villarroya J, et al. Differential effects of dolutegravir, bictegravir and raltegravir in adipokines and inflammation markers on human adipocytes. *Life Sci*. 2022;308:120948. doi:10.1016/j.lfs.2022.120948
49. Theron AJ, Anderson R, Madzime M, et al. Pro-inflammatory interactions of dolutegravir with human neutrophils in an in vitro study. *Molecules*. 2022;27(24):9057. doi:10.3390/molecules27249057
50. Vakili S, Paneru B, Guerrier CM, et al. Altered adipose tissue macrophage populations in people with HIV on integrase inhibitor-containing antiretroviral therapy. *AIDS*. 2022;36(11):1493–1500. doi:10.1097/QAD.0000000000003278
51. Jung I, Tu-Sekine B, Jin S, et al. Dolutegravir suppresses thermogenesis via disrupting uncoupling protein 1 expression and mitochondrial function in brown/beige adipocytes in preclinical models. *J Infect Dis*. 2022;226(9):1626–1636. doi:10.1093/infdis/jiac175
52. Gorwood J, Bourgeois C, Pourcher V, et al. The integrase inhibitors dolutegravir and raltegravir exert proadipogenic and profibrotic effects and induce insulin resistance in human/simian adipose tissue and human adipocytes. *Clin Infect Dis*. 2020;71(10):e549–e560. doi:10.1093/cid/ciaa259