Original Article

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Comparative safety and efficacy of BIC/FTC/TAF versus DTG+3TC in antiretroviral treatment-naive patients with HIV as first-line regimens: A real-world cohort study

Liqin Sun[1,§], Yuxin Jiang[2,§], Stephane Isnard[3,§], Jingyi Chen[4,§], Yanjun Li[5], Hui Wang[1], Fang Zhao[1], Man Rao[1], Xinyun Jia[1], Jinping Huang[5], Jinwei Wu[5], Yinsong Luo[2], Dian Zhao[2], Chenye Liu[2], Xiaorui Li[2], Jean-Pierre Routy[3,*], Jiaye Liu[2,*], Yun He[1,*], Ping Cen[5,*], Hongzhou Lu[1,*]

[1] Department of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China;
[2] School of Public Health, Shenzhen University Medical School, Shenzhen, Guangdong, China;
[3] Division of Hematology, Chronic Viral Illness Service, and Research Institute of the McGill University Health Centre, Montreal, QC, Canada;
[4] School of Medicine, Southern University of Science and Technology, Shenzhen, Guangdong, China;
[5] Laboratory of Infectious Diseases, HIV/AIDS Clinical Treatment Center of Guangxi (Nanning), The Fourth People's Hospital of Nanning, Nanning, Guangxi, China.

SUMMARY: While bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) and dolutegravir plus lamivudine (DTG+3TC) are first-line regimens for treatment-naive people with HIV (PWH), long-term real-world head-to-head comparisons of their metabolic and renal outcomes remain limited. We conducted a retrospective cohort study of ART-naive PWH initiating these regimens in China, utilizing 1:2 propensity score matching (PSM) to balance baseline covariates for 1,445 participants (901 BIC/FTC/TAF; 544 DTG+3TC). Over a 24-month follow-up, the study demonstrated comparable virologic suppression (99.7% *vs*. 100.0%; $p = 0.623$), weight changes, and cumulative incidence of metabolic abnormalities between the two groups. Conversely, although the crude 24-month incidence of eGFR decline was higher with DTG+3TC (54.8% *vs*. 40.7%; $p = 0.039$), adjusted Cox models revealed that the regimen was not independently associated with this decline (HR 1.20; 95% CI 0.97–1.48; $p = 0.18$).These findings indicate that both regimens offer comparable long-term virologic efficacy and metabolic safety profiles, supporting their routine clinical utility while highlighting the need for cautious interpretation of renal markers during integrase inhibitor-based therapy.

Keywords: antiretroviral therapy, BIC/FTC/TAF, DTG+3TC, weight change, metabolic complications, cohort study

1. Introduction

Combination antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition. Long-term goals of ART are sustained viral suppression, preservation of immunological functions, and minimization of drug-related toxicities to enable lifelong treatment (*1,2*). Over the past decade, integrase strand transfer inhibitors (INSTIs) have emerged as the cornerstone of first-line ART due to potent antiviral activity, high genetic barrier to resistance, favorable tolerability, and fewer drug–drug interactions (*3,4*).

Current international guidelines, including those from the World Health Organization (WHO), the U.S. Department of Health and Human Services (DHHS), and the European AIDS Clinical Society (EACS), uniformly recommend INSTI-based regimens as preferred first-line options for treatment-naive people with HIV (PWH). Among these, the single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) and the two-drug regimen dolutegravir plus lamivudine (DTG+3TC) are widely used, evidence-supported first-line options (*3-6*).

BIC/FTC/TAF is a once-daily fixed-dose regimen with a high genetic barrier to resistance and efficacy against hepatitis B virus (HBV). However, TAF has been associated with weight gain and alterations in lipid metabolism in both clinical trials and real-world studies (*7,8*). Although TAF generally demonstrates improved renal and bone safety compared with tenofovir disoproxil

fumarate (TDF), comparative evidence regarding renal and metabolic outcomes across contemporary INSTI-based regimens remains limited, particularly for non–tenofovir-based options and longer follow-up (*9*). DTG+3TC reduces overall antiretroviral exposure and has shown non-inferior virologic efficacy versus triple-drug regimens in randomized trials (*6-9*). However, DTG-based regimens have also been linked to weight gain and metabolic complications, raising concerns about long-term safety in routine clinical practice (*10-12*).

Thus, metabolic and renal safety are pivotal considerations when selecting INSTI-based ART (*7,10,11*). Pivotal randomized controlled trials (*e.g.* GEMINI, GS-US-380) established virologic non-inferiority for DTG+3TC and BIC/FTC/TAF, but their selected populations and trial settings may limit generalizability to clinical care (*6,7*). Real-world studies on metabolic and renal outcomes remain limited by short follow-up, modest sample sizes, or lack of direct head-to-head comparisons. Comparative evidence from China and Asia is particularly scarce, where participant characteristics, viral subtypes, comorbidity patterns, and healthcare delivery may differ from those in Western cohorts, potentially affecting the external validity of existing data.

Accordingly, we conducted a retrospective, propensity score–matched cohort study in two centers in Shenzhen and Nanning, China, to directly compare virologic and immunologic responses, as well as metabolic, hepatic, and renal outcomes between BIC/FTC/TAF and DTG+3TC among over 1400 treatment-naive PWH.

2. Methods

2.1. Study design and participants

This retrospective cohort study was conducted at the Third People's Hospital of Shenzhen and the Fourth People's Hospital of Nanning, China, the designated centers for HIV treatment and management in each city. Adults with HIV-1 who initiated ART between March 1, 2020, and May 1, 2023, were eligible if they were: (1) ART-naïve at baseline; (2) age ≥ 18 years; and (3) initiated either BIC/FTC/TAF or DTG+3TC as their first-line ART regimen. Exclusion criteria included: (1) absence of baseline HIV RNA viral load or lipid profile data; (2) history of malignancy, decompensated liver disease, or autoimmune disease at baseline; (3) active opportunistic infections at baseline; (4) pregnancy or lactation during the follow-up period; and (5) use of lipid-lowering agents at baseline.

A total of 1,697 eligible ART-naive participants were enrolled in the cohort, among whom 1,046 (61.6%) initiated BIC/FTC/TAF and 651 (38.4%) initiated DTG+3TC.

2.2. Data collection

Baseline and follow-up data were extracted from hospital electronic systems, including sociodemographic and HIV-related clinical data, ART regimen, and laboratory measurements. Under routine care, follow-up visits occurred approximately every 3 months for up to 24 months; baseline values were obtained at or immediately prior to ART initiation.

Covariates included age, sex, body mass index (BMI), time from HIV diagnosis to ART initiation, transmission route, HIV-1 RNA, $CD4^+$ and $CD8^+$ T-cell counts, weight, fasting plasma glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

2.3. Treatment regimens

Participants initiated BIC/FTC/TAF (bictegravir 50 mg, emtricitabine 200 mg, tenofovir alafenamide 25 mg; once daily) or DTG+3TC (dolutegravir 50 mg, lamivudine 300 mg; once daily) per national guidelines and clinician judgment (*13*).

2.4. Follow-up and outcomes

Participants were followed from ART initiation (baseline) for up to 24 months, with scheduled visits at approximately three-month intervals, until the end of follow-up on May 1, 2025. For time-to-event analyses, follow-up commenced 3 months after ART initiation to ensure adequate exposure time and minimize misclassification of early events. Participants were censored at the earliest occurrence of death, loss to follow-up, regimen change to a non-study ART regimen, or the end of the follow-up period. Loss to follow-up was defined as absence from scheduled visits for more than 9 consecutive months, consistent with standard clinical practice.

The primary outcomes were virologic suppression rates and longitudinal immunologic responses during follow-up. Virologic suppression was defined as an HIV-1 RNA level < 50 copies/mL (below the lower limit of detection) after ART initiation, in accordance with the 2024 Chinese Guidelines for the Diagnosis and Treatment of HIV/AIDS (*13*).

Secondary outcomes included changes in body weight and between-group differences in the cumulative incidence of metabolic and organ function-related abnormalities over the 24-month follow-up period, encompassing dyslipidemia, elevated liver enzymes, hyperglycemia, and renal dysfunction. Dyslipidemia was defined according to the 2023 Chinese Guideline for the Management of Dyslipidemia as any of the following: total cholesterol (TC) ≥ 5.2 mmol/L, triglycerides (TG)

≥ 1.7 mmol/L, LDL-C ≥ 3.4 mmol/L, or HDL-C < 1.0 mmol/L (*14*). Elevated liver enzymes were defined as ALT > 40 U/L or AST > 40 U/L, consistent with criteria established by the American Association for the Study of Liver Diseases (*15*). Hyperglycemia was defined as fasting plasma glucose ≥ 7.0 mmol/L in accordance with the 2024 Chinese Guidelines for the Prevention and Treatment of Diabetes (*16*). Renal dysfunction was defined as an eGFR < 90 mL/min/1.73 m^2 based on the National Kidney Foundation criteria (*17*).

2.5. Statistical analysis

Analyses were performed in R (v4.4.2). Propensity scores were estimated by logistic regression including age, sex, BMI, time from diagnosis to ART, transmission route, HIV RNA, $CD4^+$/$CD8^+$ counts, fasting glucose, TC, TG, LDL-C, HDL-C, eGFR, ALT, and AST. Nearest-neighbor matching used MatchIt at a 1:2 ratio without replacement (caliper 0.1).

Continuous variables were mostly summarized as medians with interquartile ranges (IQRs) and compared using the Wilcoxon rank-sum test. Categorical variables were presented as counts and percentages, with between-group comparisons performed using the χ^2 test or Fisher's exact test. Cumulative incidences of dyslipidemia, hyperglycemia, elevated liver enzymes (ALT or AST), and renal dysfunction were estimated using the Kaplan–Meier method, and between-group differences were evaluated with the log-rank test. Multivariable Cox proportional hazards regression models were employed to identify independent predictors of metabolic and renal adverse outcomes.

All statistical tests were two-sided, and a $p < 0.05$ was considered statistically significant.

2.6. Ethics statement

The study protocol was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975) and was approved by the Institutional Review Board of Shenzhen Third People's Hospital (Approval No. 2025-097-02). All participants provided written informed consent prior to enrollment.

3. Results

3.1. Baseline characteristics

Prior to PSM, several clinically relevant baseline imbalances were observed between the two treatment groups (Table 1). Specifically, participants initiating BIC/FTC/TAF were significantly younger (median age: 35 years [interquartile range, IQR: 29–45] *vs.* 43 years [IQR:32–60] in the DTG+3TC group), had a higher proportion of male participants (90.8% [950/1,046] *vs.* 84.8% [552/651]), demonstrated higher $CD8^+$ T-cell counts (857 [560–1,258] *vs.* 754 [468–1,131] cells/μL), higher eGFR (110.61 [98.13–120.17] *vs*. 103.19 [87.22–116.45] mL/min/1.73 m^2), and lower fasting plasma glucose levels (5.11 [4.78-5.53] *vs*. 5.20 [4.83-5.84] mmol/L) compared with those initiating DTG+3TC (all $p < 0.001$).

After 1:2 PSM (BIC/FTC/TAF, $n = 901$; DTG+3TC, $n = 544$), baseline covariates were well balanced (all $p > 0.05$; Table 1).

3.2. Virologic and immunologic outcomes

At the 6-month follow-up after ART initiation, virologic suppression (HIV RNA < 50 copies/mL) was achieved in 867 out of 901 participants (96.2%) in the BIC/FTC/TAF group, compared with 513 of 544 participants (94.3%) in the DTG+3TC group ($p = 0.328$). By month 12, viral suppression rates increased to 96.7% and 96.0% in the two groups, respectively ($p = 0.432$). At month 18, both groups achieved 99.3%, and by month 24, the rates were 99.7% (BIC/FTC/TAF) and 100.0% (DTG+3TC). No statistically significant intergroup differences in virologic suppression rates were observed at any of the four time points (Figure 1).

Both groups demonstrated significant increases in $CD4^+$ T-cell counts over time compared to baseline, without any statistically significant between-group differences in absolute $CD4^+$ T-cell counts at any time point (all $p > 0.05$). $CD8^+$ T-cell counts remained largely stable throughout the 24-months follow-up period between the two groups (all $p > 0.05$; Figure 2).

3.3. Weight outcome

Throughout the 24-months follow-up period, mean body weight increased modestly in both groups, from 64.35 to 67.55 kg with BIC/FTC/TAF and from 64.05 to 66.51 kg with DTG+3TC.

Between-group differences in absolute body weight at months 3, 6, 9, 12, 15, 18, 21, and 24 were not statistically significant (all $p > 0.05$; Figure 3A). Consistent with these observations, mean weight changes from baseline increased progressively over time and were numerically higher in the BIC/FTC/TAF group than in the DTG+3TC group: 1.46, 2.13, 2.43, 2.72, 2.74, 2.91, 3.02, and 3.2 kg versus 1.03, 1.38, 1.84, 2.05, 2.18, 2.17, 2.43, and 2.46 kg at months 3, 6, 9, 12, 15, 18, 21, and 24, respectively. However, between-group differences in weight change did not achieve statistical significance at any time point (all $p > 0.05$; Figure 3B).

3.4. Serum lipid profile

Both treatment groups exhibited increased lipid parameters compared with baseline. At 24 months, cumulative incidences of dyslipidemia were comparable between the BIC/FTC/TAF and DTG+3TC groups.

Table 1. Baseline Characteristics of HIV-1 Patients Before and After Propensity Score Matching (PSM)

Variables	Before PSM			After PSM		
	BIC/FTC/TAF	DTG+3TC	*p*	BIC/FTC/TAF	DTG+3TC	*p*
Total	1046	651		901	544	
Male	950 (90.8)	552 (84.8)	< 0.001	809 (89.8)	468 (86.0)	0.098
Age, yr	35 (29, 45)	43 (32, 60)	< 0.001	36 (30, 47)	38 (30, 53)	0.102
BMI,kg/m²	21.88 (19.85, 24.34)	21.60 (19.49, 24.22)	0.046	21.98 (19.84, 24.34)	21.75 (19.63, 24.45)	0.904
Route of transmission						
Heterosexual contact	418 (40.0)	357 (54.8)	< 0.001	387 (43.0)	267 (49.1)	0.097
Male-to-male sex contact	608 (58.1)	269 (41.3)		494 (54.8)	261 (48.0)	
Other	20 (1.9)	25 (3.8)		20 (2.2)	16 (2.9)	
Time from diagnosis to treatment initiation, months	14.00 (8.00, 29.75)	16.00 (9.00, 32.00)	0.032	15.00 (8.00, 31.00)	15.50 (8.00, 32.00)	0.325
HIV RNA, log copies/ml	5.19 (4.55, 5.75)	5.17 (4.58, 5.74)	0.523	5.16 (4.53, 5.71)	5.19 (4.60, 5.74)	0.432
CD4, cells/μL	230.50 (91.25, 355)	203 (53.5, 335)	0.004	225 (84, 360)	210 (67, 343)	0.384
CD8, cells/μL	857 (560, 1258)	754 (468, 1131)	< 0.001	827 (526, 1210)	780 (494.75, 1158.50)	0.15
Glucose, mmol/L	5.11 (4.78, 5.53)	5.20 (4.83, 5.84)	< 0.001	5.12 (4.79, 5.56)	5.16 (4.81, 5.64)	0.159
TC, mmol/L	4.11 (3.52, 4.74)	4.02 (3.34, 4.71)	0.015	4.12 (3.52, 4.78)	4.04 (3.40, 4.71)	0.092
TG, mmol/L	1.28 (0.95, 1.84)	1.38 (0.97, 1.99)	0.029	1.31 (0.97, 1.88)	1.35 (0.95, 2.00)	0.349
HDL, mmol/L	1.00 (0.84, 1.22)	0.99 (0.80, 1.18)	0.016	1.00 (0.84, 1.20)	1.00 (0.83, 1.19)	0.420
LDL, mmol/L	2.59 (2.10, 3.11)	2.46 (1.98, 3.01)	0.002	2.56 (2.10, 3.07)	2.46 (1.99, 3.04)	0.072
eGFR, mL/min/1.73m²	110.61 (98.13, 120.17)	103.19 (87.22, 116.45)	< 0.001	108.88 (96.53, 118.70)	106.73 (92.59, 118.48)	0.291
ALT, U/L	22.20 (15, 35)	21 (14, 34)	0.072	23 (15, 35)	21 (14, 34)	0.135
AST, U/L	23 (18, 32)	24 (18.85, 31)	0.800	23 (18.5, 32)	24 (18.45, 31)	0.779

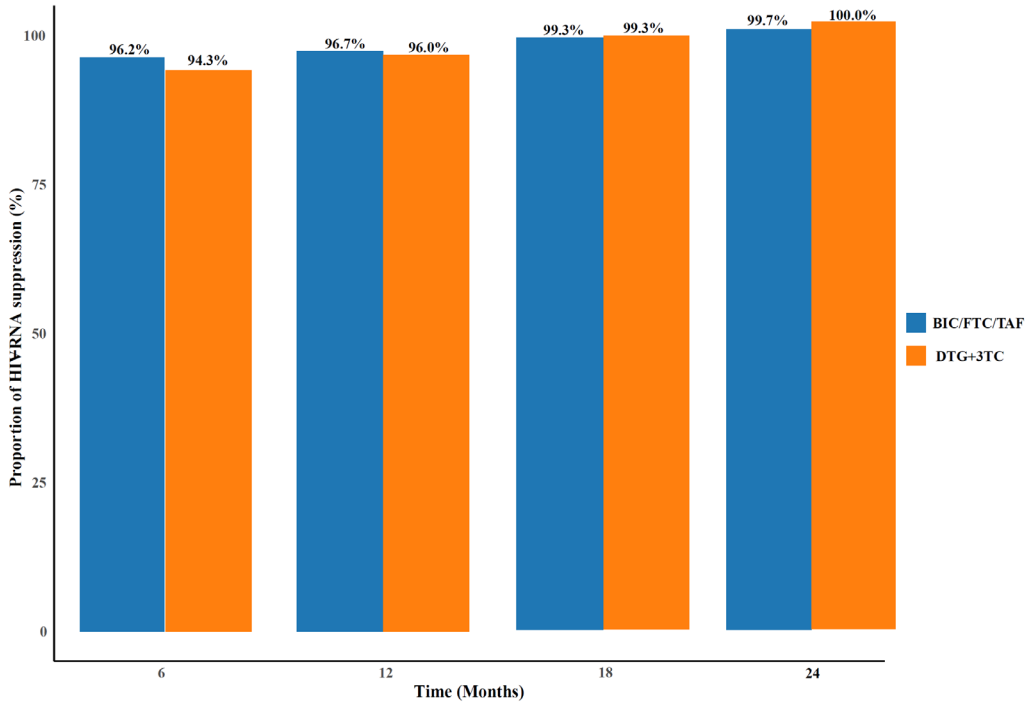

Figure 1. HIV-1 RNA suppression at 6, 12, 18 and 24 months. *Abbreviations*: BIC, bictegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; DTG, dolutegravir; 3TC, lamivudine.

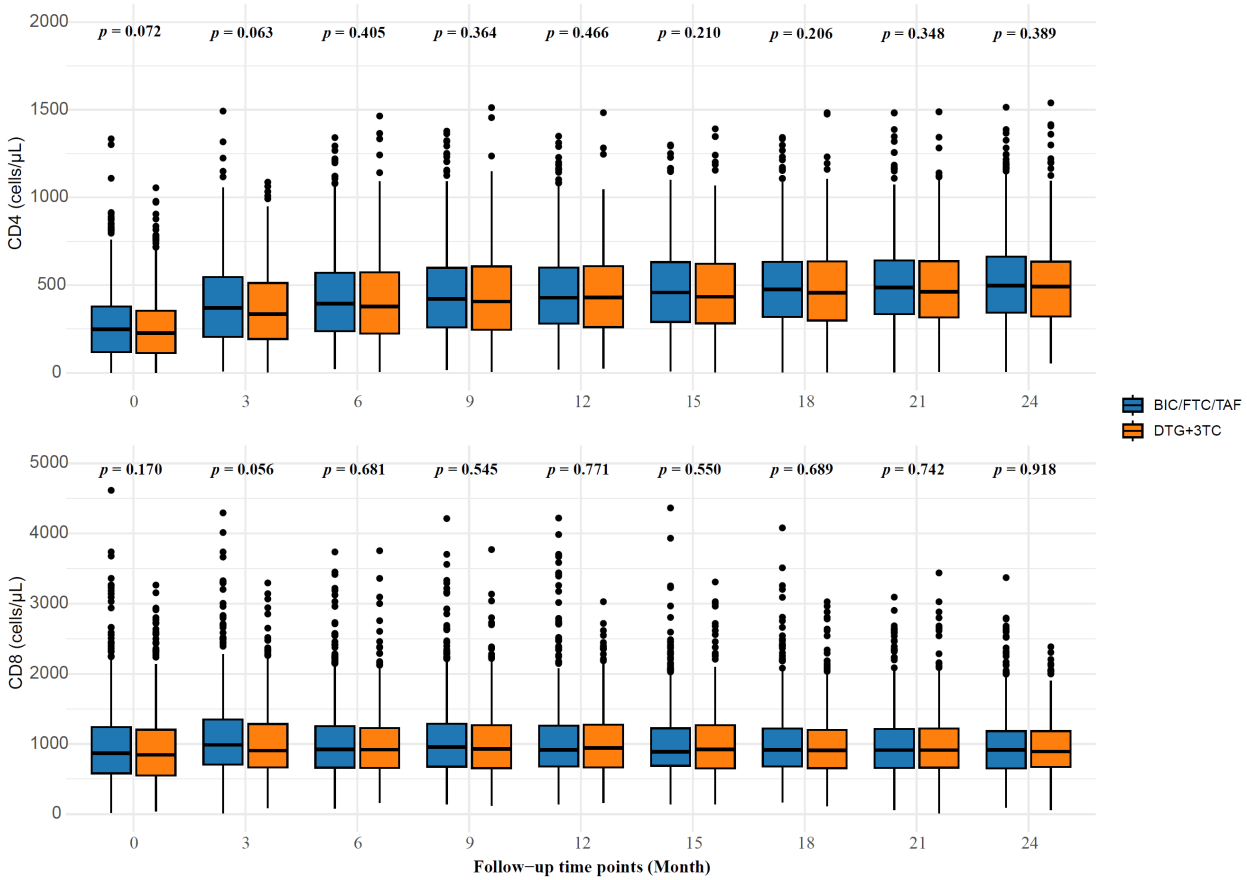

Figure 2. Longitudinal CD4⁺ and CD8⁺ T-cell counts at baseline and months 3, 6, 9, 12, 15, 18, 21, and 24. Panel A: CD4⁺ T-cell counts; panel B: CD8⁺ T-cell counts. Box and whisker plots depict the median (horizontal line), interquartile range (box), and 1.5 × IQR whiskers; individual dots represent outliers. Blue boxes correspond to participants receiving BIC/FTC/TAF, and orange boxes to those receiving DTG + 3TC. P values above each pair of boxes indicate between group comparisons at the respective time point (Wilcoxon test), none of which reached statistical significance.

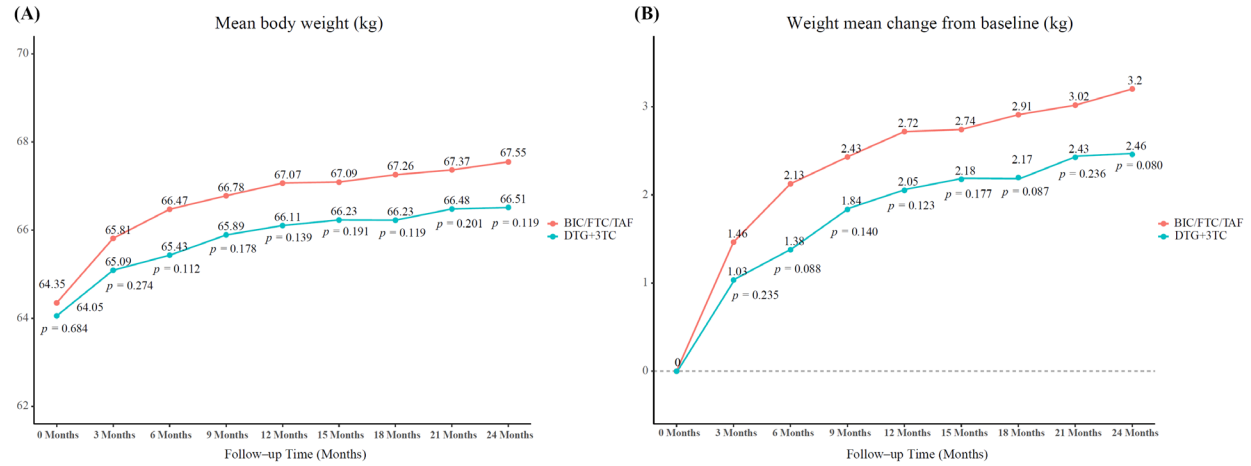

Figure 3. Longitudinal body weight measurements at baseline and at months 3, 6, 9, 12, 15, 18, 21, and 24. (A): mean body weight (kg); **(B)**: mean change from baseline (kg). Line-and-point plots represent group means at each scheduled visit; numeric labels denote the mean value (**A**) or mean change (**B**). Orange lines indicate participants receiving BIC/FTC/TAF, and blue lines represent those receiving DTG+3TC. *p*-values displayed adjacent to each time point correspond to between-group comparisons at the respective visit (pairwise derived from linear mixed-effects models); none achieved statistical significance.

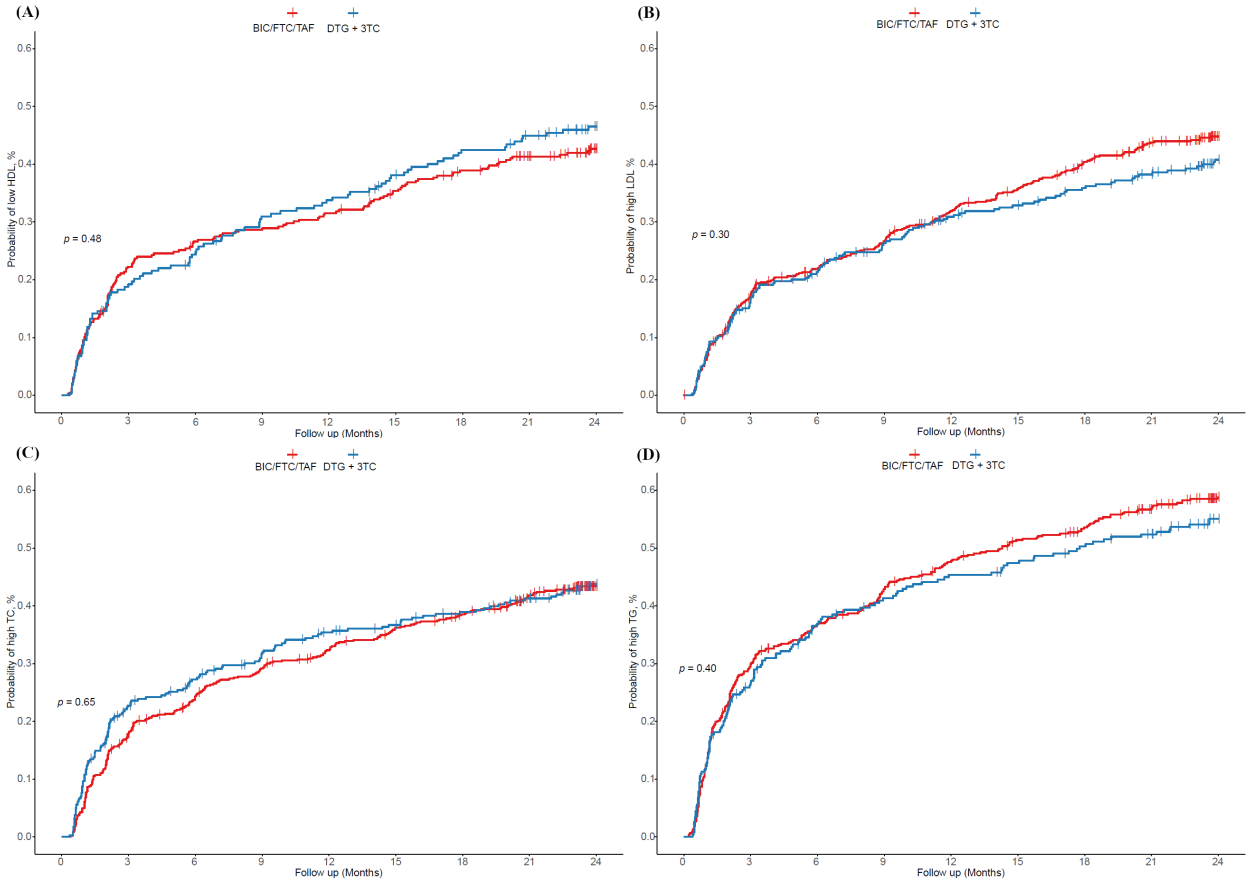

Figure 4. Kaplan-Meier survival curves illustrating the cumulative incidence of incident dyslipidemia over 24 months. Panels A – D depict the cumulative incidence of specific lipid elevations: **(A)** high density lipoprotein cholesterol (HDL-C), **(B)** low density lipoprotein cholesterol (LDL-C), **(C)** total cholesterol (TC), and **(D)** triglycerides (TG). Red curves correspond to participants receiving BIC/FTC/TAF; Blue curves represent those receiving DTG + 3TC. Shaded areas indicate 95 % confidence intervals. Intergroup differences were evaluated using the log-rank test; no statistically significant differences were observed for any lipid parameter.

Table 2. Analysis of Associated Factors for Dyslipidemia in People Living With HIV

Variables	TC		TG		LDL		HDL	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, yr	1.01 (1.00 to 1.02)	0.235	1.01 (0.99 to 1.02)	0.223	1.01 (1.00 to 1.03)	0.041	1.01 (1.00 to 1.03)	0.039
BMI, kg/m²	1.02 (0.99 to 1.06)	0.528	1.03 (1.00 to 1.05)	0.203	1.01 (0.97 to 1.04)	0.732	1.03 (0.99 to 1.06)	0.179
HIV RNA, log copies/ml	1.11 (0.98 to 1.24)	0.096	1.04 (0.94 to 1.14)	0.637	1.05 (0.94 to 1.18)	0.413	1.14 (1.02 to 1.28)	0.021
Time interval between diagnosis to initiation of treatment,mo	1.00 (1.00 to 1.00)	0.273	1.00 (1.00 to 1.00)	0.950	1.00 (1.00 to 1.00)	0.423	1.00 (1.00 to 1.00)	0.323
Sex								
Male	1		1		1		1	
Female	1.50 (1.01 to 2.25)	0.135	1.18 (0.82 to 1.70)	0.436	0.81 (0.50 to 1.32)	0.326	1.14 (0.73 to 1.78)	0.634
Route of transmission								
Male-to-male sex contact	1		1		1		1	
Heterosexual contact	1.14 (0.87 to 1.49)	0.356	1.12 (0.90 to 1.39)	0.423	0.99 (0.76 to 1.28)	0.834	0.90 (0.69 to 1.18)	0.456
Other	1.13 (0.57 to 2.24)	0.736	1.27 (0.74 to 2.17)	0.383	1.28 (0.68 to 2.39)	0.567	0.96 (0.48 to 1.91)	0.904
Glucose, mmol/L	1.11 (0.96 to 1.28)	0.255	1.05 (0.94 to 1.17)	0.366	1.09 (0.96 to 1.23)	0.377	0.99 (0.85 to 1.15)	0.875
eGFR, mL/min/1.73m²	0.99 (0.99 to 1.00)	0.107	1.00 (0.99 to 1.00)	0.095	1.00 (0.99 to 1.00)	0.421	0.99 (0.99 to 1.00)	0.123
ALT, U/L	1.00 (1.00 to 1.01)	0.085	1.01 (1.00 to 1.01)	0.012	1.00 (1.00 to 1.01)	0.373	1.01 (1.00 to 1.01)	0.038
AST, U/L	0.99 (0.98 to 1.00)	0.143	0.99 (0.98 to 1.00)	0.096	1.00 (0.99 to 1.01)	0.831	1.00 (0.98 to 1.01)	0.476
CD4, cells/μL	1.00 (1.00 to 1.00)	0.352	1.00 (1.00 to 1.00)	0.378	1.00 (1.00 to 1.00)	0.825	1.00 (1.00 to 1.00)	0.063
CD8, cells/μL	1.00 (1.00 to 1.00)	0.643	1.00 (1.00 to 1.00)	0.428	1.00 (1.00 to 1.00)	0.512	1.00 (1.00 to 1.00)	0.437
Regimen								
BIC/FTC/TAF	1		1		1		1	
DTG+3TC	1.03 (0.81 to 1.37)	0.637	1.07 (0.81 to 1.21)	0.647	1.07 (0.82 to 1.34)	0.432	0.96 (0.79 to 1.21)	0.931

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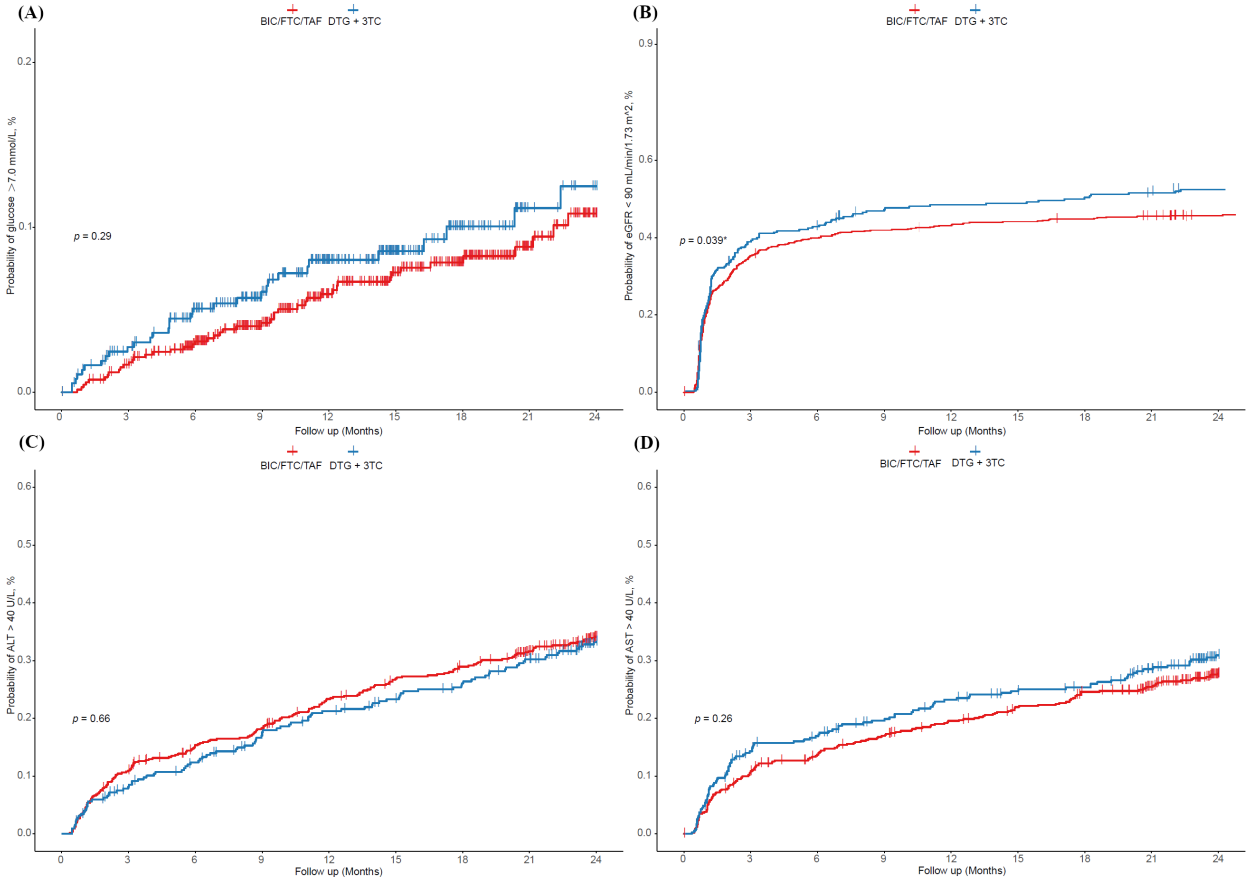

Figure 5. Kaplan-Meier survival curves depicting the cumulative incidence of incident hyperglycemia, renal dysfunction, and hepatic dysfunction over a 24-month period. (A): cumulative incidence of hyperglycemia. **(B)**: cumulative incidence of renal dysfunction (eGFR < 90 mL/min/1.73m²). **(C,D)**: cumulative incidence of hepatic dysfunction – **(C)** cumulative incidence of ALT > 40 U/L, **(D)** cumulative incidence of AST > 40 U/L.

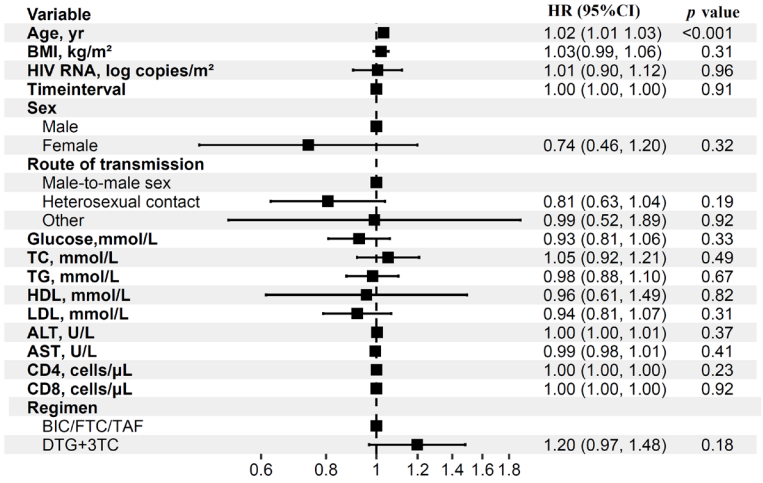

Figure 6. Multivariable predictors of eGFR < 90 mL/min/1.73 m² at 24 months. Forest plot illustrating adjusted hazard ratios (HRs) with 95 % confidence intervals derived from a Cox proportional hazards model. Each square is centered on the HR estimate and sized inversely to its variance; horizontal bars represent 95 % CIs. Variables assessed encompassed demographic factors (age, sex, transmission route), baseline clinical parameters (BMI, HIV-1 RNA, CD4 and CD8 counts), metabolic indicators (glucose, total cholesterol [TC], triglycerides [TG], high density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C]), hepatic enzymes (ALT, AST), and antiretroviral regimen (reference = BIC/FTC/TAF). Age emerged as the sole independent predictor of eGFR decline (HR 1.02 per year, 95 % CI 1.01 – 1.03; $p < 0.001$). No significant associations were detected for sex, baseline metabolic markers, or treatment regimen (DTG + 3TC *vs* BIC/FTC/TAF: HR 1.20, 95 % CI 0.97 – 1.48; $p = 0.18$). A vertical dashed line indicates the null value (HR = 1); values to the right signify elevated risk.

Specifically, incidence rates of high TC were 44.3% (95% CI 39.2–49.8%) versus 44.8% (95% CI 39.3–49.2%), high TG 59.1% (95% CI 52.3–63.4%) versus 53.2% (95% CI 48.6–59.1%), high LDL-C 46.7% (95% CI 40.2–51.2%) versus 41.3% (95% CI 36.2–47.2%), and low HDL-C 43.6% (95% CI 37.4–49.3%) versus 49.2% (95% CI 44.3–55.3%), respectively. No statistically significant between-group differences were observed (all $p > 0.05$; Figure 4A–D).

In multivariable Cox models, regimen was not associated with lipid elevations; higher baseline ALT predicted TG elevation (HR 1.01; 95% CI 1.00–1.01; $p = 0.012$), and older age predicted high LDL-C and low HDL-C (both HR 1.01; $p < 0.05$; Table 2).

3.5. Glycemic and hepatic outcomes

The cumulative incidence of hyperglycemia during follow-up was similar between the groups. By 24 months, incidence rates were 12.2% (95% CI 9.3–17.1%) in the BIC/FTC/TAF group and 14.9% (95% CI 10.2–15.8%) in the DTG+3TC group, with no statistically significant difference ($p = 0.29$; Figure 5A–B). Similarly, cumulative incidences of elevated ALT and AST were also comparable (ALT: $p = 0.66$; AST: $p = 0.26$; Figure 5C–D).

3.6. Renal outcomes

The cumulative incidence of eGFR < 90 mL/min/1.73 m² differed significantly between the treatment groups (log-rank $p = 0.039$). By 24 months, the incidence was higher in the DTG+3TC group than in the BIC/FTC/TAF group (54.8% [95% CI 49.3–59.4%] vs 40.7% [95% CI 35.9–46.3%]; Figure 5B). However, multivariable Cox regression analysis revealed that the ART regimen was not independently associated with eGFR decline. Older age was the only significant predictor (HR 1.02 per year; 95% CI 1.01–1.03; $p < 0.001$), whereas sex, body mass index, $CD4^+$ and $CD8^+$ T-cell counts, and alanine aminotransferase levels showed no significant association with risk (Figure 6).

4. Discussion

In this real-world PSM cohort study conducted at two major HIV treatment centers in China, we compared 24-month effectiveness and safety of two widely used INSTI-based first-line regimens in treatment-naive PWH. Both regimens achieved high and durable virologic suppression with parallel immunologic recovery throughout follow-up. Weight trajectories and cumulative incidence of metabolic abnormalities, including dyslipidemia, hyperglycemia, and transaminase elevations, did not differ significantly between groups. Renal outcomes were also similar after adjustment for baseline characteristics. Collectively, these findings support both regimens as viable first-line options and provide region-specific real-world evidence to guide individualized treatment selection.

We observed sustained viral suppression > 99% at 24 months in both groups, with continuous $CD4^+$ T-cell recovery and stable $CD8^+$ T-cell levels, consistent with clinical trials and real-world studies (*9,18-22*). Favorable immunologic responses may reflect participants' young age, good baseline immune status, and short interval from diagnosis to ART initiation. Our study reinforces the evidence supporting both dual-drug and triple-drug INSTI strategies as effective first-line ART strategies in Chinese PWH.

Weight gain related to ART continues to be a significant concern in PWH. In our study, weight gain occurred predominantly during the first year of therapy in both groups, followed by a deceleration phase, resulting in modest mean 24-month gains of 3.2 kg and 2.46 kg, in the BIC/FTC/TAF and DTG+3TC groups respectively (representing < 5% of baseline body weight), aligning with trials and real-world studies (*21-24*). While ADVANCE reported greater weight gain with TAF versus TDF, we only found a tendency towards greater weight gain with BIC/FTC/TAF as compared to DTG+3TC, without reaching statistical significance (*25,26*). These findings imply that weight gain during INSTI-based therapy is a multifactorial process involving return-to-health effects and lifestyle factors, rather than a regimen-specific phenomenon in the short to medium term, underscoring the importance of considering patient-level risk factors (*e.g.* sex, baseline BMI) and providing counseling and follow-up (*27,28*).

Lipid changes were modest and comparable between regimens over 24 months. These findings align with pivotal trials (TANGO, GS-US-380-4030, SALSA) and real-world data from southern China reporting mild lipid changes across INSTI strategies (*7,8,22,29*), and a retrospective comparison of continued TAF versus switching to DTG+3TC found no significant difference in LDL-C at 12 months (*30*).

Our findings highlight that TAF is unlikely to be a primary driver of dyslipidemia. Instead, lipid changes may reflect complex host-metabolic adaptations following ART initiation. In our multivariable analysis, baseline ALT, rather than regimen type, emerged as an independent predictor of lipid abnormalities. Current international guidelines do not recommend discontinuing TAF solely for lipid management. In light of the REPRIEVE trial, moderate-intensity statin therapy is advised for individuals aged 40–75 years with elevated cardiovascular risk (*4*). Although our cohort was relatively young, the substantial prevalence of lipid abnormalities highlights the necessity of routine lipid monitoring and individualized cardiovascular risk assessment. Previous research from our group further suggests that early identification of metabolic risk markers may be crucial for preventing long-term

cardiovascular events (*31-33*).

Regarding glycemic and hepatic parameters, we observed broadly comparable rates of hyperglycemia and transaminase elevations between the two regimens. These findings are consistent with international evidence indicating that INSTI-associated glycemic alterations are generally modest and often secondary to weight gain or insulin resistance rather than direct hepatotoxicity (*34-35*). Nevertheless, ongoing monitoring of glucose and liver enzymes remains warranted, particularly in individuals with metabolic syndrome, obesity, or chronic viral hepatitis, for whom even minor biochemical changes may possess greater clinical relevance.

In unadjusted analyses, the DTG+3TC group demonstrated a higher cumulative incidence of eGFR < 90 mL/min/1.73 m². However, this association was not sustained following multivariable adjustment, with age identified as the sole independent predictor of renal deterioration. This outcome suggests that patient-specific characteristics, rather than regimen-specific nephrotoxicity, likely explain the observed unadjusted disparity. Mechanistically, dolutegravir is known to inhibit tubular creatinine secretion (*36*). Therefore, modest eGFR reductions may reflect DTG alterations in creatinine handling rather than clinically significant renal impairment. Notably, employing an eGFR threshold of < 90 mL/min/1.73 m² may overestimate early renal dysfunction in relatively young and predominantly male cohorts, who typically demonstrate higher baseline eGFR values. Furthermore, this threshold may fail to capture clinically relevant deterioration. Subsequent studies incorporating more robust renal endpoints—such as eGFR < 60 mL/min/1.73 m², a ≥ 30% decline from baseline, or progression to chronic kidney disease—would provide a more clinically meaningful assessment of renal safety (*37,38*).

Several limitations warrant consideration. First, although the study utilized a multicenter design in two Chinese hospitals, its retrospective nature may limit generalizability, and residual confounding due to unmeasured variables cannot be excluded. Second, significant lifestyle and behavioral factors, including diet, physical activity, alcohol consumption, socioeconomic status, drug–drug interactions, and objective adherence metrics, were not documented and could have influenced metabolic or renal outcomes. Third, despite follow-up extending to 24 months, longer observation periods are necessary to comprehensively delineate long-term metabolic and renal trajectories. Fourth, regimen switches were handled through censoring, which might have introduced informative censoring bias if changes were driven by adverse events. Finally, the predominance of male participants may constrain applicability to women. Future prospective studies incorporating standardized lifestyle assessments and extended follow-up will be essential to further elucidate the independent metabolic and renal impacts of these regimens.

In this PSM real-world cohort study, BIC/FTC/TAF and DTG+3TC exhibited comparable virologic efficacy and overall metabolic and renal safety profiles over 24 months in more than 1400 treatment-naive PWH. These results support either regimen as an appropriate first-line option in routine clinical practice. Continued long-term studies incorporating more detailed metabolic and renal endpoints will be crucial to further clarify their long-term safety profiles in diverse populations.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Hongzhou Lu and Yun He, Department of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China.
E-mail: lluhongzhou@fudan.edu.cn (HL), yuer-he@163.com (YH)

Ping Cen, Laboratory of Infectious Diseases, HIV/AIDS Clinical Treatment Center of Guangxi (Nanning), The Fourth People's Hospital of Nanning, Nanning, Guangxi, China.
E-mail: cenping877@163.com

Jiaye Liu, School of Public Health, Shenzhen University Medical School, Shenzhen, Guangdong, China.
E-mail: liujiaye1984@163.com

Jean-Pierre Routy, Division of Hematology, Chronic Viral Illness Service, and Research Institute of the McGill University Health Centre, Montreal, QC, Canada.
E-mail: jean-pierre.routy@mcgill.ca

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