Observational Study

Medicine

OPEN

Effectiveness of integrase strand transfer inhibitors among treatment-naive people living with HIV/AIDS in Guangdong, China

A real-world, retrospective cohort study

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Abstract

Integrase strand transfer inhibitors (INSTIs) in anti-retroviral therapy (ART) have been recommended by the World Health Organization for their higher efficacy, favorable safety and tolerability. However, the clinical evidence supporting switching to INSTI-containing regimens in low-and-middle-income countries (LMICs) is limited, as few patients have access to these regimens. We aimed to assess the effectiveness of INSTI-containing regimens in real-world settings in China compared to government-provided free ART. We compared the short-term (first 4 mo following ART initiation) and long-term (1 year after ART initiation) effectiveness between INSTI-containing regimens and free ART drugs provided by the Chinese government in 4 dimensions: viral suppression status, immune response, liver and kidney function, and AIDS-related diseases. We obtained data from electronic medical records in the National Infectious Disease Surveillance System. To control baseline confounders, we used propensity score matching (PSM), calculated using logistic regression including socio-demographic and baseline factors. Among 12,836 patients from 2012 to 2019, 673 (5.2%) used INSTI-containing regimens. Patients with INSTI-containing regimens were matched to those with free drugs (644 vs 644). For short-term effectiveness, patients initiating INSTI-containing regimens were more likely to achieve viral suppression (81.4% vs 52.0%; $P < .001$). The differences in immune response, liver and kidney function and AIDS-related diseases were not significant between the 2 groups. For long-term effectiveness, viral suppression rates were similar (87.96% vs 84.59%; $P = .135$), with no significant differences in immune response, liver and kidney function, or AIDS-related diseases. Our study suggests that patients initiating ART with INSTI-containing regimens have worse physical status at baseline than patients starting with free ART drugs. Furthermore, we found better virological performances of INSTI-containing regimens in the short-term but not in the long-term due to a high rate of drug changes. Our findings have clinical implications and provide new evidence regarding the effectiveness of INSTI-containing regimens in LMICs.

Abbreviations: 3TC = lamivudine, ALT = alanine aminotransferase, ART = anti-retroviral therapy, AST = aspartate aminotransferase, DTG = dolutegravir, EFV = efavirenz, GFR = glomerular filtration rate, HCV = hepatitis C virus, INSTI = integrase strand transfer inhibitor, LMIC = low-and-middle-income country, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitors, PI = protease inhibitor, PLWHA = people living with HIV/AIDS, PS = propensity scores, PSM = propensity score matching, RAL = raltegravir, RCT = randomized clinical trial, Scr = serum creatinine, SMD = standardized mean difference, TB = tuberculosis, VL = viral load.

Keywords: acquired immunodeficiency syndrome, highly active anti-retroviral therapy, HIV, integrase inhibitors, treatment failure

MC and CL contributed to this article equally.

National Key Research and Development Program of China (2022YFC2304800), Science and Technology Project of Guangzhou (20220020276 and 2023A03J0792) and Medical Key Discipline Program of Guangzhou-Viral Infectious Diseases (2021–2023).

Patient consent was waived due to the retrospective use of electronic medical data in this study. The Institutional Review Board has passed the statement exempting informed consent.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the School of Public Health, Sun Yat-Sen University, Guangzhou, China (No. 2019-139).

Posted history: The early version of this manuscript was previously posted to Research Square: Doi: https://doi.org/10.21203/rs.3.rs-3640455/v1.

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How to cite this article: Chen M, Liu C, Xie J, Tang X, Zhang Y, Pan D, Zhong H, Du P, Li Q, Li L, Gu J, Cai W. Effectiveness of integrase strand transfer inhibitors among treatment-naive people living with HIV/AIDS in Guangdong, China: A real-world, retrospective cohort study. Medicine 2024;103:23(e38497).

Received: 21 February 2024 / Received in final form: 13 May 2024 / Accepted: 16 May 2024

http://dx.doi.org/10.1097/MD.0000000000038497

1. Introduction

In 2018, the World Health Organization recommended first-line anti-retroviral therapy (ART) regimens incorporating integrase strand transfer inhibitors (INSTIs) such as dolutegravir (DTG), bictegravir, and raltegravir (RAL) due to their higher efficacy, improved safety profile, and better tolerability.[1] Numerous randomized clinical trials (RCTs) consistently demonstrated INSTIs' superior efficacy in viral suppression and immune system restoration. An earlier RCT across 8 European countries and the United States reported an 90% viral load (VL) suppression rate for INSTI-containing regimens, compared to 83% for those containing non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) at week 48.[2] Another RCT involving 833 participants from North America, Europe, and Australia revealed an 88% viral suppression rate and a greater increase in CD4 cell count in the DTG group compared to efavirenz-containing regimens.[3] Similar conclusions were drawn from RCTs in South Africa, Uganda, and a multi-center RCT involving 566 participants across 4 continents.[4,5] However, some RCTs reported nonsignificant differences in efficacy between INSTI-containing regimens and other treatment options.[6,7] A previous RCT with 700 participants in North America reported a similar viral suppression rate (87.6% vs 84.1%) between INSTI-containing regimens and efavirenz (EFV) regimens, and this difference was not statistically significant.[6]

Real-world studies, unlike RCTs, allow us to validate the effectiveness of drug regimens in more representative patient populations.[8] However, uncontrolled confounding factors introduce greater variability in research findings regarding INSTI-containing regimens' effectiveness compared to other ART agents. A retrospective cohort study of 1388 participants conducted in the United States found that patients using INSTI-containing regimens experienced higher rates of viral suppression and achieved it more quickly compared to patients using NNRTIs and PIs.[9] Similar findings were reported in a large cohort study involving 5198 participants across Europe and Australia.[10] Conversely, a 5-year prospective cohort study of 12,585 patients in the United Kingdom showed that INSTI-containing regimens performed better in viral suppression than PIs but were more likely to result in virological failure than NNRTIs (adjusted hazard ratio: 1.25).[11] A retrospective cohort study with 495 participants in Spain found no differences between PIs, INSTIs, and NNRTIs in terms of viral suppression and immunological recovery.[12] Two retrospective studies based on the North American AIDS Cohort Collaboration on Research and Design showed INSTIs regimens had more rapid virologic response than EFV-based regimens, but the long-term virologic effect was similar[13] and similar 6-year composite clinical outcomes.[14] It's essential to note that these studies did not adequately control for confounding factors in real-world settings and relied solely on multiple regression methods for correction.

Non-randomized real-world studies are subject to more bias and confounding factors than RCTs.[8] In clinical settings, therapies may be prescribed differently based on patient and disease characteristics, leading to significant differences in baseline characteristics among patients using different ART regimens. For instance, studies have shown that patients using INSTI-containing regimens tend to be older and start ART more recently.[9,11] To address these confounding factors in observational studies based on real-world data, methods such as PSM are more effective at controlling bias compared to regression adjustments. PSM allows researchers to separate research design and analysis, assess the comparability of different treatment groups, create matched samples before analysis, and ensure an acceptable balance between the 2 groups before conducting the analysis.[15]

In 2002, China initiated the National Free Anti-retroviral Treatment Program, providing free ART drugs, including nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs, to people living with HIV/AIDS (PLWHA) for free.[16,17] Since then, ART strategies have been progressively implemented, expanded, and supplemented with improved ART drugs. The Chinese Food and Drug Administration introduced RAL and DTG in 2009 and 2015, respectively, as self-financed ART drugs. In 2018, the Chinese guidelines for the diagnosis and treatment of HIV/AIDS recommended INSTIs plus 2 NRTIs as first-line ART regimens.[18] In recent years, there has been a gradual increase in the number of PLWHA initiating ART with INSTI-containing regimens in China. Nevertheless, no studies have evaluated the effectiveness, including virological and immunological treatment responses, of INSTI-containing regimens in Chinese real-world clinical settings.

This study aims to investigate the effectiveness of INSTI-containing regimens in comparison to the free ART regimens (NRTIs, NNRTIs, and PIs) provided by National Free Anti-retroviral Treatment Program among treatment-naïve PLWHA in China. We also intend to assess and compare follow-up behavior and medication adherence during treatment between these 2 groups. Given the substantial baseline differences observed in individuals initiating ART with free drugs versus INSTI-containing regimens, we employed PSM to control for baseline confounders. Additionally, we will evaluate the long-term effectiveness of INSTI-containing regimens in comparison to the free regimens.

2. Methods

2.1. Study design and participants

This study is a retrospective cohort study using electronic medical records for real-world research. Participants in this study are PLWHA who first received ART at the Eighth People's Hospital of Guangzhou from January 1, 2012 to January 1, 2019. PLWHA were aged 18 or older and started ART for the first time with an INSTI-containing regimen (RAL or DTG) or a free drug regimen. PLWHA should have at least one follow-up record.

Ethical approval was obtained from the Institutional Review Board of the School of Public Health, Sun Yat-sen University, Guangzhou, China (No. 2019-139).

2.2. Data collection

We obtained data from electronic medical records in the National Infectious Disease Surveillance System. These records include baseline and follow-up information for PLWHA receiving treatment at designated ART clinics. Baseline and follow-up data were collected at ART initiation and subsequent scheduled follow-up visits, occurring at 1, 2, and 3 months post-ART initiation, with subsequent visits every 3 months. To assess short-term effectiveness, we tracked patients for the first 4 months following ART initiation or until regimen change, loss to follow-up, or mortality, whichever came first. This 4-month period accommodates potential delays in follow-up visits, ensuring assessment of the initial 3 follow-up appointments. The follow-up period extended until December 31, 2019, ensuring a minimum of 1 year of observation for each participant.

We collected baseline data, including socio-demographic factors (age, sex, marital status, household registration [Guangzhou or non-Guangzhou]), HIV/ART-related information (ART initiation date, time from diagnosis to ART initiation, route of HIV transmission, AIDS-related diseases [candidiasis, recurrent severe bacterial infections, herpes zoster, and other opportunistic infections excluding tuberculosis (TB)], and CD4 cell count), liver and kidney functions (glomerular filtration rate [GFR], serum creatinine [Scr], aspartate aminotransferase [AST], and alanine aminotransferase [ALT]), and comorbidities (diabetes,

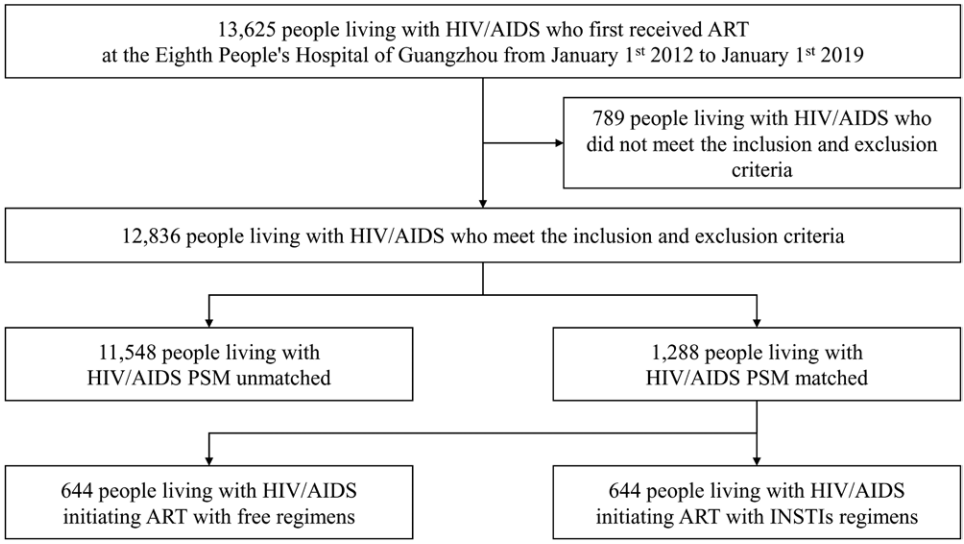

Figure 1. Flowchart of the inclusion and exclusion process of participants.

hepatitis C virus [HCV] infection, hepatitis B virus infection, and TB). During follow-up, we recorded data at each visit, including visit dates, medication adherence, ART regimens, CD4 and CD8 cell counts, VL, AIDS-related diseases, and the results of Scr, AST, and ALT.

2.3. Variables and measurement

The exposure in this study was to INSTI-containing combination regimens, with free drug combination regimens provided by the Chinese government as controls. The INSTI-containing combination regimens refer to RAL or DTG-containing regimens, and the free drug combination regimens are those regimens only use free drugs, including 8 free drugs: tenofovir, lamivudine (3TC), EFV, zidovudine, zidovudine and lamivudine, lopinavir and ritonavir, nevirapine, abacavir.

We assessed the short-term effectiveness of INSTI-containing regimens and free ART drugs across 4 aspects: viral suppression status, immunological response, liver and kidney function, and AIDS-related diseases. Viral suppression status was defined as achieving an HIV VL of < 200 HIV RNA copies/mL during the follow-up period.[19,20] Immunological response was evaluated through median CD4 cell counts at follow-up visits, whether CD4 cell counts exceeded baseline levels at the last follow-up visit, the percentage of follow-up visits with a CD4/CD8 ratio > 1, and the percentage of follow-up visits with a CD4/CD8 ratio > 1.5.[21] Liver and kidney function were determined by the percentage of follow-up visits with abnormal Scr, AST, or ALT levels. AIDS-related diseases were identified based on whether they were reported during follow-up visits and the percentage of follow-up visits with reported AIDS-related diseases among all scheduled visits. Additionally, we measured follow-up duration and adherence, defining adherence as the percentage of follow-up visits where patients were late for scheduled appointments and the percentage of follow-up visits with reported missed medication. Long-term effectiveness was evaluated using the same 4 dimensions. We also documented patients' regimen switch status and occurrences of being lost to follow-up or experiencing mortality during the observational period.

2.4. Statistical analysis

We began by presenting the baseline characteristics of the entire PLWHA sample and then separately for the 2 groups categorized by ART regimens (INSTI-containing regimens and free ART regimens). A comparison of baseline characteristics between these 2 groups was conducted. Given the significant differences observed at baseline between the groups, we employed propensity score matching (PSM) to mitigate these baseline confounding factors.[15,22] We carried out 1:1 PSM using nearest neighbor algorithms with a caliper width of 0.02. Propensity scores (PS) were generated using logistic regression. When constructing the PS model, we included sociodemographic factors (age, sex, and marital status) in addition to baseline factors that exhibited marginal significance in the comparison between patients using INSTI-containing regimens and those using free ART regimens as independent variables. The standardized mean difference (SMD) was computed to evaluate the balance of baseline confounders between the 2 groups in the matched data, with an SMD value <0.1 indicating balance.[23] Subsequently, we compared the effectiveness between INSTI-containing regimens and free ART regimens based on this balanced dataset. In all analyses, statistical significance was determined using a 2-tailed P-value < .05. The data were analyzed using R version 4.1.1.

3. Results

3.1. Result of propensity score matching and characteristics of matched sample

Figure 1 presents the study flowchart. In this analysis, we included 12,836 treatment-naïve PLWHA who initiated ART, with 673 (5.2%) of them using INSTI-containing regimens. Baseline characteristics of patients stratified by ART regimens are presented in Table 1. A total of 644 patients initiating ART with INSTIs were successfully matched to patients initiating ART with free drugs (Table 2). After matching, baseline characteristics between the 2 groups were balanced (all SMD < 0.1). In the matched sample, the average age was 42.93 ± 14.21, most patients were male (84.1%), married or cohabiting with a partner (56.4%), initiated ART after 2016 (90.1%), and began ART within 30 days after diagnosis (63.7%). About half of patients acquired HIV through sexual behavior with an opposite-sex partner (50.9%), and 41.5% had AIDS-related diseases at baseline. The median CD4 cell count was 58.0 cells/μL. Few had abnormal liver or kidney function test results. The prevalence of diabetes, hepatitis B virus infection, HCV infection, and TB were 8.5%, 13.5%, 4.3%, and 9.9%, respectively.

Table 1

Baseline characteristics of patients stratified by ART regimens.

Characteristic	All (n = 12836)	Patients with free drugs (n = 12163)	Patients with INSTIs (n = 673)	*P*
Socio-demographic status				
Age (yrs) ($\bar{x} \pm s$)	36.78 ± 12.44	36.43 ± 12.19	43.26 ± 14.87	<.001
Male	10,801 (84.1)	10,228 (84.1)	573 (85.1)	.502
Current marital status				<.001
Single	6188 (48.2)	5963 (49.0)	225 (33.4)	
Married/cohabiting with a partner	5838 (45.5)	5454 (44.8)	384 (57.1)	
Divorced/separated/widowed/unknown	810 (6.3)	746 (6.1)	64 (9.5)	
Guangzhou hukou status (yes)	3125 (24.3)	2946 (24.2)	179 (26.6)	.176
HIV/ART-related characteristics				
Initiation ART after 2016	6829 (53.2)	6215 (51.1)	614 (91.2)	<.001
Time from diagnosis to ART initiation ≤ 30 d	6672 (52.0)	6232 (51.2)	440 (65.4)	<.001
Route of HIV transmission				<.001
Sexual behavior with an opposite-sex partner	5475 (42.7)	5134 (42.2)	341 (50.7)	
Sexual behavior with a same-sex partner	6331 (49.3)	6101 (50.2)	230 (34.2)	
Injected drug use	527 (4.1)	514 (4.2)	13 (1.9)	
Other/not sure	503 (3.9)	414 (3.4)	89 (13.2)	
Presence of AIDS-related diseases[#]	2206 (17.2)	1914 (15.7)	292 (43.4)	<.001
CD4 cell count (cells/μL) [M (P_{25}, P_{75})]	233.0 (100.0, 335.0)	239.0 (118.0, 339.0)	50.0 (13.0, 164.0)	<.001
Liver and kidney function test results				
GFR (mL/min/1.73 m^2)[$]	103.7 (90.1, 118.6)	103.7 (90.2, 118.3)	103.9 (84.0, 127.6)	.630
High Scr concentration (≧133 μmol/L)	94 (0.7)	72 (0.6)	22 (2.3)	<.001
High AST concentration (≧40 U/L)	1874 (14.6)	1634 (13.4)	240 (35.7)	<.001
High ALT concentration (≧40 U/L)	2730 (21.3)	2509 (20.6)	221 (32.8)	<.001
Comorbidities				
Blood glucose (mmol/L)				.070
Normal (<6.1)	10,957 (85.4)	10,386 (85.4)	571 (84.8)	
High blood sugar (6.1–7.0)	1012 (7.9)	968 (8.0)	44 (6.5)	
Diabetes (≥7.0)	867 (6.8)	809 (6.7)	58 (8.6)	
HBsAg antibody status				<.001
Positive	1569 (12.2)	1482 (12.2)	87 (12.9)	
Negative	10,100 (78.7)	9623 (79.1)	477 (70.9)	
Never tested	1167 (9.1)	1058 (8.7)	109 (16.2)	
HCV infection				<.001
Positive	657 (5.1)	632 (5.2)	25 (3.7)	
Negative	11,054 (86.1)	10,495 (86.3)	559 (83.1)	
Never tested	1125 (8.8)	1036 (8.5)	89 (13.2)	
TB infection				<.001
Positive	634 (4.9)	568 (4.7)	66 (9.8)	
Negative	12,117 (94.4)	11,521 (94.7)	596 (88.6)	
Never tested	85 (0.7)	74 (0.6)	11 (1.6)	

ALT = alanine aminotransferase, ART = anti-retroviral therapy, AST = aspartate aminotransferase, BMI = body mass index, GFR = glomerular filtration rate, HBsAg = hepatitis B surface antibody, HCV = hepatitis C virus, INSTIs = integrase strand transfer inhibitors, Scr = serum creatinine, TB = tuberculosis.

#Including candidiasis, recurrent severe bacterial infections, herpes zoster, and other opportunistic infections expect for tuberculosis.

$GFR was calculated using Cockcroft–Gault formula standardized for body surface area.

3.2. Effectiveness and adherence of integrase strand transfer inhibitor-containing regimens and free anti-retroviral therapy drugs

We compared the effectiveness of INSTI-containing regimens and free ART drugs based on the matched sample. Short-term effectiveness and adherence are presented in Table 3. Regarding viral suppression status, patients using INSTI-containing regimens were more likely to undergo VL testing at least once compared to those using free ART drugs (13.4% vs 3.9%; $P < .001$) within the first 4 months after initiating ART. Among those who underwent VL tests at least once, patients initiating ART with INSTI-containing regimens were more likely to achieve viral suppression (81.4% vs 52.0%; $P < .001$) than their counterparts. The differences in immunological response, liver and kidney function, and AIDS-related diseases were not significant between the 2 groups. However, statistically significant differences in liver and kidney function were observed between the 2 groups in other outcomes. Among patients with normal Scr at baseline, patients using INSTI-containing regimens (n = 593), compared to those using free ART drugs (n = 576), had a higher proportion of elevated Scr during short-term follow-up (68.4% vs 53.6%; $P < .001$). Among patients with normal AST at baseline, patients using INSTI-containing regimens (n = 401), compared to those using free ART drugs (n = 394), had a lower proportion of elevated AST during short-term follow-up (52.7% vs 63.5%; $P < .001$). Among patients with normal ALT at baseline, patients using INSTI-containing regimens (n = 460), compared to those using free ART drugs (n = 433), had a lower proportion of elevated ALT during short-term follow-up (55.9% vs 63.7%; $P = .003$). Patients using INSTI-containing regimens had a shorter follow-up duration than their counterparts (2.39 [0.93, 2.87] mo vs 2.74 [1.77, 2.94] mo, $P < .001$). Regarding follow-up and medication adherence, the percentage of follow-up visits for which patients were late was lower among patients using INSTI-containing regimens than their counterparts (4.19 ± 15.59 vs 6.82 ± 20.73; $P = .021$). The percentage of follow-up visits with reported missed medication was similar between the 2 groups (Table 3).

Long-term effectiveness is reported in Table 4. The proportion of patients who underwent VL testing was similar between the 2 groups. Among those who had at least 1 VL test, the difference in viral suppression rate between the 2 groups (88.0% vs 84.7%; $P = .135$) was not significant. Immunological response,

Table 2

Characteristics of after-matching sample stratified by ART regimens.

Characteristic	All (n = 1288)	Patients with free drugs (n = 644)	Patients with INSTIs (n = 644)	SDiff
Socio-demographic factors				
Age (yrs) ($\bar{x} \pm s$)	42.93 ± 14.21	43.30 ± 13.85	42.55 ± 14.56	0.053
Male	1083 (84.1)	537 (83.4)	546 (84.8)	0.038
Current marital status				0.025
Single	437 (33.9)	215 (33.4)	222 (34.5)	
Married/cohabiting with a partner	726 (56.4)	365 (56.7)	361 (56.1)	
Divorced/separated/widowed/unknown	125 (9.7)	64 (9.9)	61 (9.5)	
Guangzhou hukou status (yes)	349 (27.1)	180 (28.0)	169 (26.2)	0.038
HIV/ART-related characteristics				
Initiation ART after 2016	1160 (90.1)	575 (89.3)	585 (90.8)	0.052
Time from diagnosis to ART initiation ≤ 30 d	820 (63.7)	401 (62.3)	419 (65.1)	0.058
Route of HIV transmission				0.029
Sexual behavior with an opposite-sex partner	656 (50.9)	332 (51.6)	324 (50.3)	
Sexual behavior with a same-sex partner	449 (34.9)	223 (34.6)	226 (35.1)	
Injected drug use	26 (2.0)	13 (2.0)	13 (2.0)	
Other/not sure	157 (12.2)	76 (11.8)	81 (12.6)	
Presence of AIDS-related diseases[#]	534 (41.5)	265 (41.1)	269 (41.8)	0.013
CD4 cell count (cells/μL) [M (P_{25}, P_{75})]	58.0 (15.0, 176.0)	68.5 (16.0, 175.3)	52.5 (14.0, 181.0)	0.082
Liver and kidney function test results				
GFR (mL/min/1.73 m^2)[$]	103.2 (84.4, 122.8)	101.7 (83.1, 118.3)	105.7 (86.0, 128.3)	0.071
Abnormal Scr concentration (≧133 μmol/L)	26 (2.0)	13 (2.0)	13 (2.0)	<0.001
High AST concentration (≧40 U/L)	434 (33.7)	216 (33.5)	218 (33.9)	0.007
High ALT concentration (≧40 U/L)	411 (31.9)	209 (32.5)	202 (31.4)	0.023
Comorbidities				0.043
Blood glucose (mmol/L)				
Normal (<6.1)	1086 (84.3)	538 (83.5)	548 (85.1)	
High blood sugar (6.1–7.0)	93 (7.2)	49 (7.6)	44 (6.8)	
Diabetes (≥7.0)	109 (8.5)	57 (8.9)	52 (8.1)	
HBsAg antibody status				0.053
Positive	174 (13.5)	89 (13.8)	85 (13.2)	
Negative	924 (71.7)	466 (72.4)	458 (71.1)	
Never tested	190 (14.8)	89 (13.8)	101 (15.7)	
HCV infection				0.048
Positive	56 (4.3)	31 (4.8)	25 (3.9)	
Negative	1068 (82.9)	533 (82.8)	535 (83.1)	
Never tested	164 (12.7)	80 (12.4)	84 (13.0)	
TB infection				0.052
Positive	127 (9.9)	67 (10.4)	60 (9.3)	
Negative	1138 (88.4)	564 (87.6)	574 (89.1)	
Never tested	23 (1.8)	13 (2.0)	10 (1.6)	

$ GFR was calculated using Cockcroft–Gault formula standardized for body surface area.

ALT = alanine aminotransferase, ART = anti-retroviral therapy, AST = aspartate aminotransferase, BMI = body mass index, GFR = glomerular filtration rate, HBsAg = hepatitis B surface antibody, HCV = hepatitis C virus, INSTIs = integrase strand transfer inhibitors, Scr = serum creatinine, TB = tuberculosis.

Including candidiasis, recurrent severe bacterial infections, herpes zoster, and other opportunistic infections expect for tuberculosis.

liver and kidney function, and AIDS-related diseases were similar between the 2 groups. Among patients with normal Scr at baseline, patients using INSTI-containing regimens (n = 598), compared to those using free ART drugs (n = 586), had a higher proportion of elevated Scr during long-term follow-up (69.6% vs 52.9%; $P < .001$). Among patients with normal AST at baseline, patients using INSTI-containing regimens (n = 405), compared to those using free ART drugs (n = 400), had a lower proportion of elevated AST during long-term follow-up (47.9% vs 57.3%; $P < .001$). Among patients with normal ALT at baseline, patients using INSTI-containing regimens (n = 464), compared to those using free ART drugs (n = 441), had a lower proportion of elevated ALT during long-term follow-up (52.4% vs 59.9%; $P = .003$). The follow-up duration was longer among patients initiating ART with free drugs than those with INSTI-containing regimens (26.96 [15.08, 38.93] mo vs 21.34 [13.97, 30.44] mo, $P < .001$). Follow-up visit adherence and medication adherence were similar between the 2 groups. Patients using INSTI-containing regimens at baseline were more likely to change their regimens during treatment than their counterparts (71.0% vs 34.8%, $P < .001$). Among those who changed ART regimens, 82.7% (378/457) of those initiating ART with INSTIs changed their regimens to free drugs, while 31.2% (70/224) of those initiating ART with free drugs changed to INSTI-containing regimens during treatment ($P < .001$). The rates of death and those who ever experienced loss to follow-up were similar between the 2 groups.

4. Discussion

This study examined the effectiveness of INSTI-containing regimens and government-provided free ART drugs among treatment-naïve PLWHA using real-world data in China. Patients initiating ART with INSTIs had a worse physical status at baseline compared to those initiating ART with free ART drugs. After controlling for baseline confounders using PSM, we found that, for short-term effectiveness, patients initiating ART with INSTI-containing regimens were more likely to achieve viral suppression than their counterparts. There were no significant differences in medication adherence between the 2 groups. For long-term effectiveness, we observed that most patients initiating ART with INSTI-containing regimens changed their regimens to free ART drugs during treatment. The viral suppression

Table 3

Short-term effectiveness and adherence of INSTI-containing regimens and free ART drugs of after-matching sample.

Outcomes	Patients with free drugs (n = 644)	Patients with INSTIs (n = 644)	*P*
Viral suppression status			
Ever tested viral load	25 (3.9)	86 (13.4)	<.001
Immunological response			
Median CD4 cell count during the follow-up visits [M (P_{25}, P_{75})]	139.0 (55.0, 259.0)	124.8 (57.8, 264.1)	.714
A higher CD4 cell count at the last follow-up visit than at baseline	537 (83.4)	558 (86.6)	.118
Percentage of follow-up visits with CD4/CD8 ratio > 1	1.11 ± 8.49	2.30 ± 13.38	.129
Percentage of follow-up visits with CD4/CD8 ratio > 1.5	0.09 ± 1.64	0.56 ± 5.86	.094
Liver and kidney function (%) ($\bar{x} \pm s$)			
Percentage of follow-up visits with high Scr concentration[a]	1.72 ± 12.62	2.41 ± 14.24	.127
Percentage of follow-up visits with high AST concentration[b]	22.42 ± 34.55	19.70 ± 33.73	.086
Percentage of follow-up visits with high ALT concentration[c]	31.30 ± 39.28	27.22 ± 36.99	.078
AIDS-related diseases			
Whether AIDS-related diseases were reported	53 (8.2)	44 (6.8)	.398
Percentage of follow-up visits with reported AIDS-related diseases	4.26 ± 16.19	3.28 ± 13.65	0.329
Follow-up duration and adherence			
Follow-up duration (mo) [M (P_{25}, P_{75})]	2.74 (1.77, 2.94)	2.39 (0.93, 2.87)	<.001
Percentage of follow-up visits for which the patient was late	6.82 ± 20.73	4.19 ± 15.59	.021
Percentage of follow-up visits with reported missed medication	6.66 ± 19.87	5.36 ± 17.63	.218

ALT = alanine aminotransferase, ART = anti-retroviral therapy, AST = aspartate aminotransferase, GFR = glomerular filtration rate, INSTIs = integrase strand transfer inhibitors, Scr = serum creatinine.

[a]serum creatinine (Scr) concentration ≥ 133 μmol/L.

[b]aspartate aminotransferase (AST) concentration ≥ 40 U/L.

[c]alanine aminotransferase (ALT) concentration ≥ 40 U/L.

Table 4

Long-term effectiveness of INSTI-containing regimens and free ART drugs of after-matching sample.

Outcomes	Patients with free drugs (n = 644)	Patients with INSTIs (n = 644)	*P*
Viral suppression status			
Ever tested viral load	515 (80.0)	532 (82.6)	.253
Immunological response			
Median CD4 cell count during the follow-up visits [M (P_{25}, P_{75})]	204.0 (115.0, 334.4)	207.0 (126.1, 353.1)	.247
A higher CD4 cell count at the last follow-up visit than at baseline	474 (94.8)	480 (94.1)	.737
Percentage of follow-up visits with CD4/CD8 ratio > 1	3.73 ± 13.84	4.84 ± 16.88	.575
Percentage of follow-up visits with CD4/CD8 ratio > 1.5	0.89 ± 6.75	0.97 ± 6.42	.783
Liver and kidney function (%) ($\bar{x} \pm s$)			
Percentage of follow-up visits with high Scr concentration[a]	1.32 ± 9.03	2.75 ± 14.25	.076
Percentage of follow-up visits with high AST concentration[b]	14.83 ± 24.29	12.82 ± 21.70	.217
Percentage of follow-up visits with high ALT concentration[c]	23.62 ± 29.20	20.84 ± 26.71	.197
AIDS-related diseases			
Whether AIDS-related diseases were reported	97 (15.8)	93 (15.0)	.748
Percentage of follow-up visits with reported AIDS-related diseases	2.89 ± 9.90	2.49 ± 8.65	.701
Follow-up duration and adherence			
Follow-up duration (mo) [M (P_{25}, P_{75})]	26.96 (15.08, 38.93)	21.34 (13.97, 30.44)	<.001
Percentage of follow-up visits for which the patient was late	11.31 ± 20.17	10.33 ± 17.62	.705
Percentage of follow-up visits with reported missed medication	12.34 ± 19.41	10.43 ± 16.38	.212
Regime switch			
Had changed ART regimes during follow-up	224 (34.8)	457 (71.0)	<.001
Follow-up status			
Death	49 (7.6)	50 (7.8)	1.000
Whether lost to follow-up was reported	89 (13.8)	95 (14.8)	.691

ALT = alanine aminotransferase, ART = anti-retroviral therapy, AST = aspartate aminotransferase, GFR = glomerular filtration rate, INSTIs = integrase strand transfer inhibitors, Scr = serum creatinine.

[a]serum creatinine (Scr) concentration ≥ 133 μmol/L.

[b]aspartate aminotransferase (AST) concentration ≥ 40 U/L.

[c]alanine aminotransferase (ALT) concentration ≥ 40 U/L.

rate and immunological response were similar between the 2 groups.

The groups using INSTI-containing regimens and free ART drugs had distinct baseline characteristics. The choice of ART regimens was influenced by state of illness, drug adverse effects, economic factors, and so on. In our study, INSTI-containing regimens were more commonly prescribed to PLWHA with worse physical status which is consistent with previous studies in the UK and US.[11,24] This preference may be due to increasing evidence supporting superior immunological and virological responses with INSTI-containing regimens from clinical trials.[3,7] Clinicians may favor INSTI-containing regimens for patients with worse physical conditions and comorbidities. Since the introduction of RAL and DTG in China, the number of PLWHA using INSTI-containing regimens has steadily increased. However, we found that approximately seventy percent of patients initiating ART with INSTI-containing regimens switched to free ART regimens during treatment. This finding contrasts with a previous study conducted in Japan that reported a low switch rate of INSTI-containing regimens.[25] PLWHA initiating ART with INSTI-containing regimens in China are required to pay for their medications (approximately 151 USD

and 294 USD per month for DTG and RAL), which can pose a significant financial burden for most patients in China and other low-and-middle-income countries (LMICs). Therefore, the switch rate of INSTI-containing regimens was relatively high in our study, with most patients transitioning to free ART regimens during treatment.

In our study, the virological treatment response to INSTI-containing regimens was better than free ART drugs, consistent with RCT studies,[3,7,21] meta-analysis,[26] and some observational cohort studies.[9,10] However, a UK cohort study of 12,585 participants using real-world data found that the INSTIs group had a 1.52 times greater risk of virological failure compared to NNRTIs.[11] This discrepancy may be due to unmeasured or uncontrolled confounders, such as medication adherence. In our study, we achieved balance in observed baseline characteristics between the 2 groups in the matched data, and medication adherence at follow-up visits was similar. Although the differences were not significant, we also found that patients initiating ART with INSTI-containing regimens had a higher CD4/CD8 ratio, a lower rate of abnormal liver function test results, a higher rate of abnormal kidney function test results, and a lower rate of AIDS-related diseases during treatment after ART initiation. These findings align with previous studies, indicating lower side effects and higher efficacy of INSTI-containing regimens.[4,27] The higher rate of abnormal kidney function test results may be due to the physiological increase in creatinine caused by INSTIs drugs, which does not necessarily indicate actual kidney impairment but could be a result of the drug's impact on muscle tissue.

The lack of significant differences may be attributed to the small sample size, reduced by PSM in this study. The comparison of the proportions of Scr, AST, and ALT during follow-up higher than that at baseline between the 2 groups also helps illustrate this point. Future cohort studies with larger sample sizes and multiple centers are warranted to investigate the effectiveness of INSTI-containing regimens in real-world settings in LMICs. We found that patients using INSTI-containing regimens were more likely to be late for scheduled follow-up visits. This result highlights the need for healthcare workers to focus on improving follow-up adherence for patients using INSTI-containing regimens.

In our study, the long-term ART effectiveness between those initiating ART with INSTI-containing regimens and those with free ART regimens was similar. This finding may be explained by the fact that most INSTI-containing regimen users changed their regimens to free ART drugs during treatment. Future studies can evaluate the availability of INSTI-containing regimens in LMICs and conduct cost-effective analyses.

Several limitations must be considered when interpreting our results. First, although we chose the largest ART clinic in South China as our study site, our study was not a multicenter cohort study, and the sample's representativeness and generalizability was limited.[28] Second, our data were derived from electronic medical records, and although we used PSM to control for baseline confounders, there may still be residual confounders that were not measured at baseline. Third, we could not compare the effectiveness of INSTI-containing regimens and free ART regimens among those with relatively better physical status at baseline, as most of the patients using INSTI-containing regimens had relatively worse physical status in our study.

5. Conclusion

To our knowledge, our study was the first to assess the effectiveness of INSTI-containing regimens using real-world clinical data in China. We found better virological performance of INSTI-containing regimens compared to free ART regimens among treatment-naïve PLWHA during the first 4 months of ART. However, this advantage of INSTI-containing regimens disappeared in the long-term due to the high rate of regimen changes. Our study has clinical implications and provides new evidence regarding the effectiveness of INSTI-containing regimens in LMICs.

Author contributions

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