PASS INFORMATION

Title	Post-marketing study to assess the effectiveness of doravirine included in highly active antiretroviral therapy (HAART) in Chinese adults living with HIV-1
Version identifier of the final study report	MK1439-088/VERSION 1.0
Date of last version of the final study report	Not applicable
EU PAS register number	EUPAS103993
Active substance	Doravirine tablets (PIFELTRO™):100 mg of doravirine Doravirine, lamivudine, and tenofovir disoproxil fumarate tablets (DELSTRIGO™): 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate
Medicinal product	PIFELTRO™ (MK-1439) and DELSTRIGO™ (MK-1439A)
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN, Haarlem, The Netherlands
Joint PASS	No
Research question and objectives	The objective of this non-interventional study is to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1.
Country(-ies) of study	China
Author	Prof. Hao Wu Beijing You An Hospital, Capital Medical University PPD PPD, Biostatistical and Research Decision Sciences (BARDS) Epidemiology, MSD R&D (China) Co., Ltd PPD
Sponsor Final Repository (REDS) Date	13-FEB-2025

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN, Haarlem, The Netherlands
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1 ABSTRACT

Title

Post-marketing study to assess the effectiveness of doravirine included in highly active antiretroviral therapy (HAART) in Chinese adults living with HIV-1

Keywords

PIFELTRO™, DELSTRIGO™, HIV-1, Virologic Suppression, Medical Chart Review

Rationale and background

PIFELTRO™ and DELSTRIGO™ were approved in China on 24-Nov-2020 and 29-Dec-2020 separately. CCI [redacted]

This study is proposed to fulfill the post marketing requirement on effectiveness information collection CCI [redacted]

Research question and objectives

Primary objective: to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1;

Secondary objective: to describe demographic, clinical characteristics, and treatment patterns of study population.

Study design

A retrospective multicenter observational study using medical chart review.

Setting

Data for this study was obtained via secondary data collection from 7 hospitals in which PIFELTRO™ or DELSTRIGO™ were available during the study period. The study key information included study-related demographic, clinical (including medical history, diagnosis history and viral load [VL]) and treatment information (including combination antiretroviral therapy [cART] regimens and discontinuation).

Subjects and study size, including dropouts

The study population consisted of Chinese adults living with HIV-1 receiving doravirine included in HAART. The study planned to evaluate ~210 study participants, thus about 350 participants had to be included with an estimated evaluability rate of 60%. Assuming 60% ~

90% of participants achieving virologic suppression (VS, HIV-1 RNA<50 copies/mL) at week 48±8, the width of 95% confidence interval (CI) ranged from 13.2% to 8.2%.

Variables and data sources

Variables

Exposure: PIFELTRO™ and DELSTRIGO™ treatment

Primary outcome: VS (HIV-1 RNA< 50 copies/mL) achieved at week 48±8 following PIFELTRO™ and DELSTRIGO™ administration

Secondary outcomes: HIV-1 treatment patterns

Data Sources

Relevant individual-level information was collected from multiple information systems, including the Electronic Medical Record (EMR)/paper medical records, Hospital Information System (HIS), Laboratory Information System (LIS), and routine clinical management material from clinicians in selected hospitals.

Results

A total of 358 participants were enrolled from August 2nd 2021 to June 21st, 2024, whereas 6 participants were excluded from the study population for pre-existing resistance to Non-nucleoside Reverse Transcriptase Inhibitor (NNRTIs) and other drugs included in Antiretroviral Therapy (ART) after enrolled. Therefore, the study population consisted of 352 participants. Among them, 271 participants were included in the effectiveness analysis population since they had data available to confirm the achievement of VS at week 48±8, and 81 participants were excluded from the effectiveness analysis population due to lack of data to inform effectiveness at week 48±8 (9 participants discontinued PIFELTRO™ or DELSTRIGO™, 68 participants missed VL testing result at 48 ± 8 weeks, and 4 participants used an unqualified HIV-1 RNA test with the lower limit of detection >50 copies/mL at week 48±8).

Among the effectiveness analysis population of 271 participants, the mean age at baseline was 39.8 years. Higher proportions of the effectiveness analysis population were male (85.6%), from west region (78.6%) and paid by insurance covering DELSTRIGO™ (86.7%). There were total 211 ART experienced participants, of whom 72 ART experienced participants (34.1%) had available VL data within 30 days prior to the index date (the date of the first treatment of PIFELTRO™ or DELSTRIGO™), including 66 participants (91.7%) with VL<50 copies/mL, 3 participants (4.2%) with VL ≥50 and ≤400 copies/mL and 3 participants (4.2%) with VL >400 copies/mL. There were total 60 ART naïve participants, of whom 57 ART naïve participants (95%) had available VL data within 30 days prior to the index date, including 48 participants (84.2%) with VL <100,000 copies /mL and 9 participants (15.8%) with VL ≥100,000 copies/mL. The demographics and baseline

characteristics were similar between the study population and the effectiveness analysis population.

Among ART experienced participants, the most common regimen within 1 year before the index date in the effectiveness analysis population was dual Nucleoside Reverse Transcriptase Inhibitor (NRTI)+NNRTI (81.0%) , followed by dual NRTI/1 NRTI+integrase strand transfer inhibitor (INSTI) regimen (10.9%), dual NRTI+Protease Inhibitor (PI) regimen (6.6%) and others (1.4%). A total of 44 experienced participants (20.9%) had at least one change in cART regimen during 1-year prior to index date. The cART regimen used in the study population before the index date was similar to that of the effectiveness analysis population.

Most participants (98.9%) were administrated with DELSTRIGO™ as doravirine based regimen, and only 3 participants (1.1%) were treated with PIFELTRO™ and DELSTRIGO™ in different time periods in the effectiveness analysis population. No participants only used PIFELTRO™ for 48±8 weeks. No significant difference of doravirine based regimen pattern between the effectiveness analysis population and study population.

A total of 9 (2.6%) participants discontinued of PIFELTRO™ or DELSTRIGO™ treatment. Only 4 participants were documented the reasons for discontinuation, which included 1 participant with poor drug tolerance, 1 participant with financial situation, and other two participants with others. The proportions of participants with adherence ≥80% was 91.5% (248/271) during the period of 48±8 weeks in the effectiveness analysis population.

Among 271 participants (211 ART experienced and 60 ART naïve participants) included in the effectiveness analysis population, the proportion of VS was 93.7% (254 participants, 95% CI: 90.8%, 96.6%) at week 48±8. Only 17 participants didn't achieve VS , of whom 14 participants (82.4%) were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant (5.8%) was confirmed to have VL >200 copies/mL (285 copies/mL), and 2 participants (11.8%) were confirmed to have VL >1000 copies/mL (19,959 and 26,500 copies/mL) at week 48±8 (noting that in the 2 participants who had VL >1000 copies/mL the adherence for 48±8 weeks was 54% and 64% respectively, which is likely to contributed to the unachieved VS at week 48±8).

Among the 248 participants with adherence ≥80% during the period of 48±8 weeks, the proportion of VS was 94.0% (95% CI: 91.0%, 96.9%). Only 15 participants didn't achieve VS at week 48±8, of whom 14 participants (93.3%) were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant (6.7%) was confirmed to have VL >200 copies/mL (285 copies/mL).

Among 60 ART naïve participants and 211 ART experienced participants regardless of VS at baseline, 90.0% (54/60, 95% CI: 82.4%, 97.6%) of ART naïve participants and 94.8% (200/211, 95% CI: 91.8%, 97.8%) of ART experienced participants achieved VS at week 48±8, respectively. Of 6 naïve participants without achieving VS at week 48±8 (all the participants with adherence ≥80%), all the 6 participants had no genotypic drug resistance testing at baseline, and 2 participants were found to be resistant to NNRTI class (efavirenz [EFV] and nevirapine [NVP]) after 6 months of doravirine-containing treatment. Of 11

experienced participants without achieving VS at week 48±8, 6 participants (54.5%) had no drug resistance testing and unknown VL at baseline (including 1 participant with low adherence rate of 54%), 3 participants (27.3%) had no drug resistance testing and had VL<50 copies/mL at baseline, 1 participant (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and had VL<50 copies/mL at baseline, and 1 participant (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and unknown VL with adherence rate of 64%. No significant difference in the proportion of VS was observed between the naïve and the experienced participants.

The study also conducted sensitivity analysis to assess the impact of different ways of evaluating VL (HIV-1 RNA) within week 48±8 on primary endpoint, including: 1) While participants with multiple virologic results at week 48±8 could only use the result closest to 48-week time point (±8 weeks) for the primary analyses, in the sensitivity analysis 1, the last available virologic result for a participant with multiple virologic results at week 48±8 was used for VS estimation. The result showed only 1 participant belonged to the scenario described and was included in the sensitivity analysis 1, ultimately 94.1% (95% CI: 91.3%, 96.9%) of participants achieved VS. 2) In the sensitivity analysis 2, it would include participants for whom an assay with lower limit of detection (LLOD) of 100 copies/mL was used and who had VL <100 copies/mL at baseline (indicating VS before doravirine [DOR] initiation), but would exclude someone for whom an assay with LLOD of 50 copies/mL was used and who had a VL between 51 and 99 copies/mL. The result showed 4 participants belonged to the scenario described and were included in the sensitivity analysis 2, ultimately 94.3% (95% CI: 88.8%, 99.7%) of ART experienced participants who could be confirmed VS before DOR initiation achieved VS at week 48±8. 3) In the sensitivity analysis 3, it used the adherence cutoff of at least 95% instead of 80% for VS estimation (a subgroup analysis population that used the adherence cutoff). The result showed 31 participants belonged to the scenario described and were excluded from the sensitivity analysis 3, ultimately 94.0% (95% CI: 90.9%, 97.2%) of participants achieved VS.

Among all the included participants, DELSTRIGO™ and PIFELTRO™ were well tolerated, 5.1% (18/352) of the participants had nonserious AEs. No SAE or severe AEs were reported during the study period.

Discussion

In the present study, with the inclusion and exclusion criteria consistent to the approved labels, the doravirine-containing HAART is confirmed to be an effective treatment in Chinese adults living with HIV-1 regardless of VL at baseline in China. Among the participants who were administered PIFELTRO™ or DELSTRIGO™, it achieved the VS rate of 93.7% after 48±8 weeks' treatment. Similar results have been observed in ART naïve and experienced participants (90.0% for ART naïve participants and 94.8% for ART experienced participants regardless of VS before DOR initiation). Above results show that they are similar to or higher than the point estimates in pivotal clinical trials no matter in treatment-naïve participants (84% of PIFELTRO™ in DRIVE-FORWARD, 84.3% of DELSTRIGO™ in DRIVE-AHEAD) or in treatment-experienced participants (90.8% of DELSTRIGO™ for participants with VL <50 copies/mL at baseline in DRIVE-SHIFT).

Doravirine-containing HAART has also shown consistent effectiveness in adults living with HIV-1 in other real-world studies. In the UK, using similar retrospective chart review study design, 90% (9/10) of ART naïve participants and 95% (244/256) of ART experienced participants treated with DOR-containing ART had an undetectable VL (<50 copies/mL) at 6 months [Ref. 5.4: 08RF7W].In France, in 50 highly ART-experienced participants with long-term VS, DOR/lamivudine (3TC) regimens can maintain high levels of VS (98.0%) at week 48, CD4+ T cell count was also restored [Ref. 5.4: 08RF7P]. Another study from Italy retrospectively investigated 132 participants who switched to DOR-containing/-based regimens, the proportion of undetectable HIV-1 RNA was 94.3% (49/52) at week 24, and confirmed a favorable impact from DOR on lipid profile and a neutral impact on weight gain [Ref. 5.4: 08RF7Z]. A national prospective cohort from the Netherlands (ATHENA National Observational Cohort Study) assessed the effectiveness of switching to DOR based ART in well suppressed participants without previous virologic failure, showing non-inferior compared with continuing non-DOR-containing regimens after 2 years in a real-world setting [Ref. 5.4: 08RF83]. In Spain, at week 48 the effectiveness of DOR plus two NRTI was between 73.3% and 90.8% for experienced participants with 91% of VS at baseline by intention-to-treat analysis, where non-complete or missing data were considered treatment failure [Ref. 5.4: 08RF7S]. In another real-world study of NNRTI class conducted in China, e.g., ainuovirine (ANV) plus two NRTIs showed 83.6% of VS at week 48 among 122 ART naïve participants [Ref. 5.4: 08RF7D].

One of the limitations of this study is that the included hospitals were not randomly selected and may not be a representative sample of the total Chinese participants administered with PIFELTRO™ or DELSTRIGO™. The hospital selection was based on the operation difficulty, potential number of people living with HIV (PLWH) and potential use of PIFELTRO™ or DELSTRIGO™. This study aims to select hospital with more potential PLWH and use of PIFELTRO™ or DELSTRIGO™ to meet the target sample size. One of the main strengths of this multicenter study is the large sample size of participants in a real-life clinical setting rather than a clinical trial in China. Moreover, data were from clinical records of all the available participants receiving PIFELTRO™ or DELSTRIGO™ at seven hospitals and the investigators contacted all eligible participants unselectively until enrollment completion. All the participants who signed informed consent or were authorized informed consent exemption by Institutional Review Board/Ethics Review Committee (IRB/ERC) had been included in our study. In summary, though the study has some limitations, it is unlikely to have a big impact on the effectiveness evaluation and the generalizability of the study results.

This is the first post-marking observational study conducted in China to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. Doravirine-containing HAART has shown an high overall effectiveness, that was estimated as 93.7% (95% CI: 90.8%, 96.6%) at week 48±8 in Chinese persons living with HIV-1, including ART naïve and ART experienced participants regardless of VS at baseline in this study, which is consistent with that reported in previous overseas studies in real-world settings.

Marketing Authorisation Holder(s)

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Names and affiliations of principal investigators

Prof. Hao Wu, Beijing You An Hospital, Capital Medical University, China

2 LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANV	ainuovirine
ART	Antiretroviral Therapy
cART	Combination Antiretroviral Therapy
CDE	Center for Drug Evaluation
CI	confidence interval
CRF	Case report form
D4T	stavudine
DAA	Direct Acting Antivirals
DDI	didanosine
DOR/3TC/TDF	doravirine/lamivudine/tenofovir disoproxil fumarate
DRV/c	darunavir/cobicistat
DTG	dolutegravir
EFV	efavirenz
EMR	Electronic Medical Record
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FDC	fixed-dose combination
FI	Fusion Inhibitor
FTC	emtricitabine
GPP	Good Pharmacoepidemiology Practice
HAART	Highly Active Antiretroviral Therapy
HGRAC	Human Genetic Resource Administration of China
HIS	Hospital Information System
HIV	Human Immunodeficiency Virus
HOI	health outcome indicator
ICF	informed consent form
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
LIS	Laboratory Information System
LLOD	lower limit of detection
LPV/r	lopinavir/ritonavir

NFV/r	nelfinavir/ritonavir
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
non-AIDS	non-acquired immunodeficiency syndrome
NRDL	National Reimbursement Drug List
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAR	non-serious adverse reaction
NVP	nevirapine
PCR	Polymerase Chain Reaction
PI	Protease Inhibitor
PLWH	People Living with HIV
PQC	product quality complaint
Q1	the first quartile
Q3	the third quartile
RAL	raltegravir
RCT	Randomized Controlled Trial
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SD	Standard Deviation
SOP	Standard Operating Procedure
SQI	Significant Quality Issue
TDF	tenofovir disoproxil fumarate
TFL	tables/figures/listings
TND	target not detected
VL	Viral Load
VS	Virologic Suppression

3 INVESTIGATORS

Principal investigator	Prof. Hao Wu, Beijing You An Hospital, Capital Medical University, China
Coordinating investigator for each country in which the study is to be performed	Not applicable
Sponsor contacts	PPD MSD R&D (China) Co., Ltd.
Other contacts	PPD MSD R&D (China) Co., Ltd.
Vendor/Collaborator	CO-CRO Medical Development Co., Ltd
Investigators	PPD, Beijing You An Hospital, Capital Medical University, China PPD, Beijing Ditan Hospital, Capital Medical University, China PPD, Shanghai Public Health Clinical Center, China PPD, Public Health Clinical Center of Chengdu, China PPD, Yunnan Provincial Hospital of Infectious Disease, China PPD, Kunming Third People’ s Hosptial, China PPD, Guiyang Public Health Rescue and Treatment Center

4 OTHER RESPONSIBLE PARTIES

Shared Responsibilities	Contact Person
CO-CRO Medical Development Co., Ltd	PPD

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	July 2023	25-07-2023	NA
End of data collection	Approximately 3 months prior to start of compilation of study report	21-06-2024	NA
Registration in the EU PAS register	NA	23-03-2024	Updated on 07-05-2024
Final report of study results	CCI [redacted]	13-FEB-2025	NA

6 RATIONALE AND BACKGROUND

Background

Human immunodeficiency virus (HIV) is the etiologic agent of acquired immunodeficiency syndrome (AIDS). Ongoing infection with HIV remains a serious challenge to health. If left untreated, HIV targets the immune system by depletion of CD4+ T cells, leading ultimately to AIDS, opportunistic infections, and death. In 2020, the global burden of HIV/AIDS was 37.7 million cases, corresponding to 0.5% of the world's population, and the total number of new infections and AIDS-related deaths was 1.5 million and 0.68 million, respectively [Ref. 5.4: 084J97].

The HIV infection (mainly HIV-1 infection) epidemic in China has evolved significantly over the past 35 years and it remains a major public health problem. The number of newly diagnosed cases has increased each year from 41 thousand in 2004 to 135 thousand in 2017. At the end of 2020, there were 1.053 million people living with HIV and 351,000 cumulative reported deaths in China [Ref. 5.4: 084HLB].

The use of combination antiretroviral therapy (cART) prevents the depletion of CD4+ T cells, resulting in restoration of the immune system. cART has changed HIV infection from a fatal illness to a chronic disease. At the end of 2020, 978,138 (92.9%) out of the total of 1.053 million PLWH in China were receiving antiretroviral therapy (ART), 96.1% of those on ART were able to achieve virologic suppression [Ref. 5.4: 084HLB].

Currently, there are more than 30 individual drugs and fixed-dose combinations available for the treatment of HIV infection. These agents belong to six distinct mechanistic classes known as reverse transcriptase inhibitors (nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs], nonnucleoside reverse transcriptase inhibitors [NNRTIs]), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (CCR5 co-receptor antagonists), and integrase strand transfer inhibitors (INSTIs).

Updated Chinese guidelines for diagnosis and treatment of HIV/AIDS (2021 edition) recommend initiating ART in treatment naïve persons with a regimen consisting of two NRTIs along with a third antiretroviral agent from NNRTI class, PI class or INSTI class, while single-tablet regimen offers persons with additional options [Ref. 5.4: 084HM7]. The recommendations from the IAS-USA Antiretro-viral Guidelines on initial antiretroviral regimens, including an INSTI plus 2 NRTIs, or NNRTI/ boosted PI plus 2 NRTIs [Ref. 5.4: 084HLD].

Doravirine (DOR, tradename PIFELTRO™) is an NNRTI that is indicated in combination with other antiretroviral medicinal products for the treatment of adults living with HIV-1 without resistance to the NNRTI class. Doravirine, lamivudine, tenofovir disoproxil fumarate (DOR/3TC/TDF, tradename DELSTRIGO™) is a fixed-dose combination indicated for the treatment of adults living with HIV-1 without past or present evidence of resistance to the NNRTI class, lamivudine and tenofovir. As one of the highly efficacious and well tolerated NNRTIs, active against both wild type virus and most common NNRTI resistant variants at concentrations achieved with once daily dosing, PIFELTRO™ and DELSTRIGO™ have

been approved in more than 50 countries, such as the US, EU, Canada, Switzerland, Australia, etc. PIFELTRO™ and DELSTRIGO™ were approved in China in 24-Nov-2020 and 29-Dec-2020, respectively.

PIFELTRO™ can be taken without regard to food and has a low potential for drug–drug interactions, including with acid-reducing drugs. In the randomized, controlled, double-blind, multicenter, non-inferiority, phase-3 trial conducted at 125 clinical centers in 15 countries (DRIVE-FORWARD), 769 participants were randomly assigned to treatment (385 with PIFELTRO™ and 384 with ritonavir-boosted darunavir), with two investigator-selected NRTIs. At week 48, 321 (84%) antiretroviral-naïve participants in the PIFELTRO™ group and 306 (80%) in the darunavir group achieved plasma HIV-1 RNA of less than 50 copies per mL (difference 3.9%, 95% CI: 1.6, 9.4), indicating non-inferiority of the doravirine-containing regimens to ritonavir-boosted darunavir-containing regimens. The change in CD4+ T cell counts from baseline to week 48 was also similar in the two treatment groups. PIFELTRO™ was generally well tolerated up to 48 weeks of treatment [Ref. 5.4: 05RFGF]. At week 96, a higher proportion of the PIFELTRO™ group (277 [73%] of 383) achieved an HIV-1 RNA concentration of less than 50 copies per mL than did those in the darunavir group (248 [66%] of 383; difference 7.1%, 95% CI: 0.5, 13.7) [Ref. 5.4: 05FFRK]. In another phase 3, double-blind, non-inferiority trial at 126 sites worldwide (DRIVEAHEAD), antiretroviral treatment–naïve adults with ≥1000 HIV-1 RNA copie/mL were randomized (1:1) to either DELSTRIGO™ or EFV/FTC/TDF. At week 48, 84.3% (307/364) of DELSTRIGO™ recipients and 80.8% (294/364) of EFV/FTC/TDF recipients achieved <50 HIV-1 RNA copies/mL (difference 3.5%, 95% CI: -2.0, 9.0), which demonstrated noninferior efficacy of DELSTRIGO™ to EFV/FTC/TDF [Ref. 5.4: 0580VV]. The efficacy of switching from a baseline regimen (consisting of two NRTIs in combination with a ritonaviror cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or an NNRTI) to DELSTRIGO was evaluated in a randomized, open-label trial (DRIVE-SHIFT). Subjects must have been virologically suppressed (HIV-1 RNA <50 copies/mL) on their baseline at which point they switched to DELSTRIGO. At week 48, 90.8% (406/447) on DOR/3TC/TDF had HIV-1 RNA < 50 copies/mL, demonstrating noninferiority vs Baseline Regimen at week 24 [difference -3.8 (-7.9 to 0.3)]. Of the 209 participants in the Baseline Regimen who switched to DOR/3TC/TDF at week 24, 198 (94.7%) had HIV-1 RNA<50 copies/mL at week 48 [Ref. 5.4: 05B4PY].

Rationale

PIFELTRO™ and DELSTRIGO™ were approved in China on 24-Nov-2020 and 29-Dec 2020 separately. CCI [redacted]

To fulfill the post marketing requirement on effectiveness information collection, the sponsor proposed to conduct a retrospective multicenter observational study to assess the effectiveness of doravirine included in highly active antiretroviral therapy (HAART) in Chinese persons living with HIV-1. People living with HIV/AIDS go to a local designated hospital to access ART and other treatments in China. Therefore, the HIV treatment mode presents the feature of persons accumulation in the designated hospital. PLWH are more likely to be retained in care at the hospital where they initiate treatment. Based on the preliminary assessment of the potential number of participants prescribed doravirine included in HAART in several infectious disease hospitals, as well as the medical treatment mode mentioned above, it is feasible to conduct a retrospective observational study with these designated hospitals as study sites. In addition, the retrospective observational study design would help to get the effectiveness data of the product in Chinese population as early as possible.

Another advantage of the observational study using medical chart review is that the effectiveness study can be conducted without any intervention, which would obtain information on persons receiving doravirine included in HAART to better reflect real-world clinical practice. It is the most feasible way to take electronic medical records as the basic data source in research methods. CCI [redacted]

7 RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1 by a retrospective observational study design using medical chart review.

7.1 Primary Objectives

To assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. The effectiveness were evaluated at week 48±8 among participants who have data available to confirm the achievement of virologic suppression (VS, defined as plasma HIV-1 RNA less than 50 copies per mL at week 48±8) after 48±8 weeks' treatment of PIFELTRO™ or DELSTRIGO™.

7.2 Secondary Objectives

Among Chinese adults living with HIV-1 who has been treated with PIFELTRO™ or DELSTRIGO™:

To describe demographic and clinical characteristics, including:

- Demographic characteristics at baseline;

- Clinical characteristics including medical history, diagnosis history and VL, specifically the;
    - Medical history including comorbidities and concomitant medications on index date* and during the 48±8 weeks observation period;
    - Diagnosis history including date of HIV diagnosis and participants type receiving cART;
    - Viral load (HIV-1 RNA) at key time points, including baseline period, week 48±8 and any follow-up visits during the observation period.

To describe HIV-1 treatment patterns among the study population, including:

- cART regimens during the 1-year prior to index date and the 48±8 weeks observation period;
- Discontinuation of PIFELTRO™ or DELSTRIGO™ treatment during the 48±8 weeks observation period.

*Index date is defined as the date of the first treatment of PIFELTRO™ or DELSTRIGO™.

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
None				

9 RESEARCH METHODS

9.1 Study design

The study did not involve any interventional measurements, e.g., receiving oral doravirine, laboratory test for CD4+ T cell count and viral load. Under the protocol, all participants accepted ART previously in the course of routine clinical practice.

The design was a retrospective multicenter observational study using medical chart review. Adult living with HIV-1 (>=18 years old) who had been treated by PIFELTRO™ or DELSTRIGO™ in accordance with National Medical Products Administration (NMPA)'s approved product information were potential subjects for the study. After inclusion/exclusion criteria check, the participants who had continued PIFELTRO™ or DELSTRIGO™ for 48±8 weeks and have VL data at 48±8 weeks were evaluated, and all the information was collected through retrospective medical chart review including but not limited to outpatient or inpatient medical records, lab reports, prescription records, etc., by qualified investigators.

Effectiveness was evaluated as the proportion of participants achieving VS who continued PIFELTRO™ or DELSTRIGO™ for 48±8 weeks and had VL data at 48±8 weeks. The proportion was calculated as the number of participants achieving VS at week 48±8 divided by the number of participants who had VL data at 48±8 weeks (included participants with VS and virologic failure [defined as continuous plasma viral load of >200 copies/mL after 24 weeks of treatment, or detectable viral load of ≥200 copies/mL after achieving virologic suppression]).

The demographic, clinical characteristics and HIV-1 treatment patterns were described in this study.

9.2 Setting

The hospitals in which PIFELTRO™ or DELSTRIGO™ were available since August 2021 (the earliest month recorded for PIFELTRO™ or DELSTRIGO™ prescription) and had the most persons using these two products during the study period were considered.

Site selection depended on the potential eligible participants number, willingness of principal investigator to participate, the completeness of medical records on study key information as well as the feasibility assessment from the operational perspective. According to the marketing investigation, majority of these two drugs were prescribed in 8-10 designated hospitals for PLWH.

A total of 7 sites were selected for the study, including 1 leading site and 6 sub-sites as below:

Leading Site:

- 01 Beijing You An Hospital Capital Medical University, Beijing, China

Sub-Sites:

- 02 Beijing Ditan Hospital Capital Medical University, Beijing, China
- 03 Shanghai Public Health Clinical Center, Shanghai, China
- 05 Public Health Clinical Center of Chengdu, Chengdu, Sichuan Province, China
- 07 Yunnan Provincial Hospital of Infectious Disease, Kunming, Yunan Province, China
- 08 Kunming Third People′ s Hosptial, Kunming, Yunan Province, China
- 09 Guiyang Public Health Rescue and Treatment Center, Guiyang, Guizhou Province

The study was conducted retrospectively with data collection starting from July 25th 2023 (start of data collection) and ending on June 21st 2024 (end of data collection). Specifically, it included participants accrual period (August 2nd 2021 [the first participant started PIFELTRO™ or DELSTRIGO™] to September 30th 2023 [the last participant started

PIFELTRO™ or DELSTRIGO™]), observation period (August 2nd 2021 to June 21st 2024 [the last participant enrolled]) and data extraction period (July 31th 2023 to September 18th 2024).

9.3 Subjects

The study population consisted of adults living with HIV-1 started receiving doravirine included in HAART during participants accrual period in all 7 study sites. The participants who met all the inclusion criteria and failed to meet any exclusion criterion were included in the study.

- **Inclusion criteria**
  - Chinese and resident in China, i.e., Chinese descent born in China, and have a Chinese home address
  - New users of PIFELTRO™ or DELSTRIGO™
  - At least 18 years of age on the day of initiating PIFELTRO™ or DELSTRIGO™
- **Exclusion criteria**
  - Off-label treatment with PIFELTRO™ or DELSTRIGO™ (as approved in China), including the following criteria:
    1) Pregnancy on index date, or breast-feeding on index date
    2) For those participants treated with DELSTRIGO™, documented CrCl <50 mL/min on index date
    3) For those participants treated with PIFELTRO™ or DELSTRIGO™, documented end-stage renal disease, undergoing dialysis or severe hepatic impairment (Child-Pugh Class C) on index date
  - Participating in any clinical trial (interventional)
  - Has documented or known resistance to NNRTIs and other drugs included in ART prior to initiation of PIFELTRO™ or DELSTRIGO™
  - There is a written reason of doravirine included in HAART termination due to the national reimbursement drug list (NRDL) adjustment in China in the early 2022

9.4 Variables

9.4.1 Exposure

The study exposure of interest is PIFELTRO™ or DELSTRIGO™ treatment. However, this study did not involve the active PIFELTRO™ or DELSTRIGO™ treatment. The study

included participants who received PIFELTRO™ or DELSTRIGO™ treatment in routine clinical practice.

Participants were also assessed among the following sub-groups based on their exposure to ART based on any available data, which included: prescription documented in medical record, dispensing records:

- ART naïve adults
- ART experienced adults with or without VS

9.4.2 Outcome

9.4.2.1 Primary Outcomes

The primary outcome was VS achieved at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration.

Laboratory measurements of HIV-1 RNA testing were extracted from the chart review of the medical records. Only quantitive VL (HIV-1 RNA) measurement or qualitative measurement with a limit of 50 copies/mL or lower (e.g., <40 copies/mL or <20 copies/mL) was used to determine the VS.

Participants with continuous use of PIFELTRO™ or DELSTRIGO™ during the observation period were included in the VS calculation. This included participants with virologic failure before week 40 (The virologic failure is designated by investigators and documented in EMR/paper medical records), but those who met the definition of treatment discontinuation (evidence of ≥60-day gap in treatment, definition of "treatment discontinuation" see 9.4.2.2.2) were not included in the assessment.

9.4.2.2 Secondary Outcomes

In support of the secondary objectives, the study reported the following demographic, clinical characteristics and HIV-1 treatment patterns in the study population.

9.4.2.2.1 Demographic Variables at Baseline

- Year and month of birth
- Age
- Gender
- Height and weight
- Smoking
- Alcohol use

- Geographic region (e.g., rural/urban, eastern/middle/western)
- Type of medical insurance
- Insurance coverage for PIFELTRO™ or DELSTRIGO™

Clinical Variables

Medical History

- Comorbidities
- Presence of concomitant medications (e.g., hepatitis drugs [direct acting antivirals (DAA)], calcium supplements, rifabutin, dabrafenib)

Diagnosis History

- Date of HIV-1 diagnosis
- Participant type receiving cART (naïve/experienced)
- Pregnancy (yes/no)
- Breast-feeding (yes/no)
- Death date

Laboratory Measures (Viral Load)

For each testing result：

- Testing date of HIV-1 RNA VL
- Lab testing methods at local laboratory for HIV-1 RNA including reverse transcription polymerase chain reaction (RT-PCR), NASBA or real-time Polymerase Chain Reaction (PCR) (e.g., Abbott Real-time HIV-1 assay)
- VL within 30 days prior to index date, at week 48±8 and any time during the observation period
- Qualitative measurement of VL

9.4.2.2.2 HIV-1 Treatment Patterns

cART Regimen Related Variables

- Class of ARTs prior to PIFELTRO™ or DELSTRIGO™ administration

- Description of all previous ARTs in experienced participants (including anchor agent class [including NNRTIs, PIs, INSTIs or fusion inhibitor], background NRTIs, pill burden [e.g., single tablet regimen, multiple tablet regimen])
- Evidence on the resistance to NNRTIs prior to PIFELTRO™ or DELSTRIGO™ administration
- Evidence on the resistance to other drugs included in cART except NNRTIs prior to PIFELTRO™ or DELSTRIGO™ administration
- Description of doravirine based regimen (including background NRTIs, pill burden [e.g., single tablet regimen, multiple tablet regimen])
- Evidence of PIFELTRO™ or DELSTRIGO™ prescription (e.g., date of prescription, dosing instructions, prescription duration)

Discontinuation of PIFELTRO™ or DELSTRIGO™ Treatment

- PIFELTRO™ or DELSTRIGO™ discontinuation (yes/no)
- Stop date of PIFELTRO™ or DELSTRIGO™ treatment (date when previously dispensed medications were expected to be finished or documented by the clinician in medical records)
- VL at discontinuation

A ≥60-day gap for PIFELTRO™ or DELSTRIGO™ was considered as discontinuation of treatment. Participants who restarted PIFELTRO™ or DELSTRIGO™ treatment after a ≥60-day gap remained classified as discontinued. It was identified as documented by the clinician in medical records or calculated as a minimum 60-day gap between the prescription refill date and the date when previously dispensed medications were expected to be finished. A change in backbone alone didn't constitute discontinuation (i.e., the change of 3TC or TDF can't be regarded as discontinuation).

When a participant was considered to have discontinued PIFELTRO™ or DELSTRIGO™ treatment, the below categories were classified as the reason for discontinuation:

- Prior treatment failure (including resistance, VL ≥200, etc.)
- Drug-drug interactions (e.g., potential, actual)
- Tolerability
- Financial (e.g., insurance coverage)
- Simplification
- Pregnancy

- Others (cannot be free text)
- Not documented

9.4.3 Covariates

Due to the retrospective chart review design, it is unlikely to access each participant's data of prescribed medication for the entire period since the index date in the hospitals in China. Thus, adherence was not considered when calculating the effectiveness endpoint. However, adherence was used in sub-group analysis to investigate whether using the adherence would lead to a difference in effectiveness results.

9.4.3.1 Adherence

Calculation of Adherence

Adherence was assessed for 48±8 weeks periods, which was calculated as the pills they have been prescribed divided by the total pills they should be prescribed over the whole period [Ref. 5.4: 084HLG]. Specifically, for the time interval between the last prescription and HIV viral load testing, the pills prescribed should be regarded as been taken by participantss and added in the numerator.

Adherence was only calculated for DOR in the regimen or DELSTRIGO™.

Medication Variables

The following medication variables was recorded for each participant between index date until week 48±8 following PIFELTRO™ or DELSTRIGO™ treatment, discontinuation or death before week 48±8:

- Date of prescription
- Prescription dose
- Dosing instructions
- Duration between the two prescriptions (days)

9.5 Data sources and measurement

During the site initiate visit, the source of each variable was confirmed with the investigators of each site, and the "Confirmation Form of Original Data from Site" was signed. All source data comes from the following source files.

Variable List by Domain	Data source
Demographic information, participant inclusion and exclusion criteria information, laboratory testing (VL, drug resistance), participant's comorbidities information, participant's concomitant medication information	EMR/paper medical records, HIS, LIS /paper laboratory test report, routine management material from clinicians, confirmation form for inclusion and exclusion criteria
Prescription information for PIFELTRO™ or DELSTRIGO™	EMR/paper medical records, routine management material from clinicians
Participant's HIV diagnosis and treatment history	EMR/paper medical records, HIS, routine management material from clinicians, HIV diagnosis report

9.5.1 Study Procedures

This study does not involve active administration of PIFELTRO™ or DELSTRIGO™. The study protocol was submitted for approval by the institutional review board (IRB)/ethics review committee (ERC).

Exemption from obtaining written informed consent under certain conditions for this study was authorized in 6 sites, except Public Health Clinical Center of Chengdu. The study was also approved by the Human Genetic Resources Administration of China (HGRAC) for International Cooperation Study. Medical chart review initiated in sites from July 31st 2023 when the first participant who had available data of VL at week 48±8 was enrolled in study. The medical chart review ended on September 18th 2024 when the overall study enrollment goal was achieved, no matter how many participants for each site had been accrued. With the use of a standardized case report form (CRF), demographics, clinical and treatment information was extracted from medical charts by trained staff.

9.6 Bias

As this is an observational study, potential bias can’t be ruled out. Data collection reflected routine clinical practice rather than mandatory assessments at prespecified time points, which may have an impact on the amount of data available and its interpretation. Potential sources of bias as well as strategies to minimize these are discussed further below.

As this is not a comparator effectiveness study and not designed to compare specifically PIFELTRO™ or DELSTRIGO™ treatment with other cART regimens. With this design the VS may be over- or underestimated, due to factors such as adherence, persistence and possible unknown resistance to NNRTIs and other drugs included in ART, as well as unavailability of VL at week 48±8 to be included due to return visit irregularly to miss VL testing (non-respondent/survivor/information bias). To mitigate the bias, the following actions were implemented. Based all the available potential participants in EMR, the study contacted all eligible participants who had been treated for at least 24 weeks unselectively until enrollment completion, and all the participants who signed informed consent form (ICF) or were authorized informed consent exemption by IRB/ERC were included in our study. In addition, any evidence related to resistance to NNRTIs, and other drugs included in ART was searched based on multiple data sources to avoid including participants with resistance to NNRTIs.

Second, the selected hospitals were not randomly selected and may not be a representative sample of the whole PIFELTRO™ or DELSTRIGO™ administrated participants (selection bias). The hospital selection was based on the operation difficulty, potential number of participants and potential use of PIFELTRO™ or DELSTRIGO™. This study aims to select hospital with more potential participants and use of PIFELTRO™ or DELSTRIGO™ to present the representativeness.

Third, unlike the study medication diary in clinical trials, adherence through the prescription monitoring would result in inaccurate measurement of adherence. For example, participants may forget refill, drop the medicine or forget to take after refill, which were regarded as adherence through the prescription monitoring (information bias). Thus, the study was designed not to use data from prescription monitoring for the effectiveness endpoint calculation but only use for sensitivity analysis. In clinical practice, clinicians usually conducted routine participants management to remind participants to take the medicines regularly, which helped to mitigate the bias to some extent.

9.7 Study size

The study planned to evaluate ~210 participants, thus about 350 participants had to be included with an estimated evaluability rate of 60%. Assuming 60% ~ 90% of participants achieving VS at week 48±8, the width of 95% CI would ranged from 13.2% to 8.2%. Below table shows the width of 95% CI for this sample size.

Proportion of participants achieving VS	Proportion of participants achieving VS	Width
60%	53.4%-66.6%	13.2%
70%	63.8%-76.2%	12.4%
75%	69.1%-80.9%	11.8%
80%	74.6%-85.4%	10.8%
85%	80.2%-89.8%	9.6%
90%	85.9%-94.1%	8.2%

9.8 Data transformation

The geographic region was categorized into the following four major geographic regions: East (including Beijing, Tianjin, Hebei, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan), Central (including Shanxi, Anhui, Jiangxi, Henan, Hubei, and Hunan), West (including Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet (Xizang), Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang), and Northeast (including Heilongjiang, Jilin, and Liaoning). Refer to the economic zones defined by the National Bureau of Statistics: https://www.stats.gov.cn/hd/cjwtjd/202302/t20230207_1902279.html.

Comorbidity was be based 8 categories including cardiovascular and renal diseases, liver diseases, cancers, non-acquired immunodeficiency syndrome (non-AIDS) and AIDS-defining cancer, mental health and pain conditions, lung diseases, autoimmune diseases, endocrine disorders and gastrointestinal diseases.

In the ART naïve participants, VL was categorized as "<100,000 copies/mL" and "≥100,000 copies/mL". In the ART-experienced participants, VL was categorized as "<50 copies/mL", "≥50 copies/mL and ≤400 copies/mL", and ">400 copies/mL".

PIFELTRO™ or DELSTRIGO™ prescription was categorized as: (1)Doravirine tablets (PIFELTRO™); (2)Doravirine, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (DELSTRIGO™); (3)PIFELTRO™ and DELSTRIGO™ combined (for dose adjustment, e.g., with rifabutin); (4)PIFELTRO™ and DELSTRIGO™ in different time periods.

The HIV-1 treatment regimen was categorized into the following groups based on the drug classes selected in the CRF: (1) Dual NRTI+NNRTI; (2) Dual NRTI+PI; (3) Dual NRTI/NRTI+INSTI; (4) PI+INSTI; (5) Others.

Drug resistance is a derived variable. If a participant was resistant to NNRTIs, NRTIs, PIs or INSTIs, the participant was considered as drug resistance.

9.8.1 Data management

All data management activities including data capture, data storage, data cleaning, data security, and system backup processes were undertaken by qualified personnel and followed all procedures detailed in a separate "Data Management Plan".

In this study, data management activities included, but were not limited to security, programming, systems and data validation, sequencing of operational steps and events, quality assurance and data backup. These procedures were intended to ensure the authenticity, integrity, and confidentiality of electronic records.The study complied with Good Pharmacoepidemiology Practice (GPP), and applicable laws and regulations relating to the conduct of the study.

9.9 Statistical methods

9.9.1 Main summary measures

A descriptive analysis of the distribution of values abstracted for each variable was provided. For the continuous variables we are interested in, the values of mean/median, standard deviation (SD), min/max, interquartile range (IQR, including the first quartile [Q1] and third quartile [Q3]) were calculated; the frequency and percentages were calculated for these categorical variables. Statistical comparisons were conducted using chi-square test for categorical variables and Student's *t*-test, Mann-Whitney U test, Kruskal-Wallis H test for continuous variables as appropriate. All analyses were carried out using all available data. A participant with missing data on one variable was used only in calculations that do not involve that variable.

A separate detailed statistical analysis plan (SAP) and corresponding mock-up tables/figures/listings (TFL) was developed and finalized prior to conduct of any analyses in this study, and the plan was developed using GPP principles for conducting observational studies.

9.9.2 Main statistical methods

Primary objective(s)

Number and proportion of participants with VS at week 48±8 were calculated with a 95% CI in ART naïve and experienced Chinese adults living with HIV-1 with up to 48±8 weeks' treatment. The denominator denoted the number of participants who had data available to confirm the achievement of VS after 48±8 weeks' treatment of PIFELTRO™ or DELSTRIGO™, including:

- Participants who achieved VS at week 48±8;
- Participants who had viral load testing result without achieving VS at week 48±8;
- Participants who were confirmed as virologic failure before week 40.

HIV virologic information denoted plasma HIV-1 RNA quantitive/qualitative results. If the qualitative assay has a lowest limit of the detection of 200/500 HIV-1 RNA copies/ml of plasma, it was excluded from the primary analysis. Any participants who had only one available HIV virologic information at week 48±8 and laboratory test results closest to 48-week time point (±8 weeks) was used for the primary analyses. The participants with evidence of discontinuation (except virologic failure before week 40) during the observation period should be excluded for the primary analyses.

A subgroup analysis of an adherence cutoff of at least 80% was used if data was available. Results were also stratified by participants sub-groups based on exposure to ART at the time of PIFELTRO™ or DELSTRIGO™ initiation:

- ART naïve participants vs. ART experienced participants with or without VS
- ART naïve participants and ART experienced participants without VS vs. ART experienced participants with VS

Secondary objective(s)

Baseline Demographic and Clinical characteristics

The variables (Section 9.4.2.2 [Secondary outcomes]) were described among participants in the study population overall, and separately by participants included and excluded from the effectiveness analyses. The variables were also described among ART naïve and experienced Chinese persons living with HIV-1, separately. Baseline demographic, baseline clinical characteristics (including comorbidities and VL) among ART naïve and experienced Chinese persons living with HIV-1 were compared.

HIV-1 treatment patterns

The variables (Section 9.4.2.2 [Secondary outcomes]) were described among participants in the study population overall, and separately by participants included and excluded from the effectiveness analyses.

For doravirine-containing HAART discontinuation characteristics, frequency, proportion of participants with discontinuation, and time taken from the initiation to discontinuation were reported. The reason for discontinuation was classified and reported.

Additionally, descriptive analyses of adherence including medication variables were reported.

9.9.3 Missing values

Any missing value was handled as a missing value and no imputation was carried out. A participant with missing data on one variable was used only in calculations that did not involve that variable. This allows analysis with larger sample sizes than when using complete datasets on all variables.

9.9.4 Sensitivity analyses

- To assess the impact of different measurements of VL (HIV-1 RNA) on primary endpoint, sensitivity analyses were conducted.
    - Sensitivity analysis 1: According to the Food and Drug Administration (FDA) guidance on how to determine the timepoint of virologic outcome

[Ref. 5.4: 04DT6Q] , assuming that virologic outcome should be assessed based on the last available measurement while the participant was on treatment and continued on the trial within the time window was therefore the most compliant with the FDA guidance for VS estimation.

- Sensitivity analysis 2: Considering only one available VL measurement (HIV-1 RNA) at baseline of less than 100 copies/mL based on qualitative assay was common, assuming that all baseline VLs (HIV-1 RNA) for these ART-experienced participants were less than 50 copies/mL (indicating VS), these participants were classified into the ART-experienced participants with VS group prior to the initiation of DOR for the analysis of VS estimation in the subgroup.

- Sensitivity analysis 3: Considering an adherence cutoff of at least 95% was used for all the participants with available prescription information, this analysis aimed to investigate whether adherence levels would result in differences in VS estimation.

For all the sensitivity analysis, please refer to the analysis for evaluating the primary objective.

9.9.5 Amendments to the statistical analysis plan

Not applicable in this study.

9.10 Quality control

In the whole process, all parties agreed to following applicable standard operating procedures (SOPs). All parties also agreed to ensuring all existing and new study personnel were appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GPP, and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor conducted routine management meeting with CO-CRO, reviewed the data management plan and statistical analysis plan, conducted audit visits to ensure oversight and conduct of the study were completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. There was no significant quality issue (SQI) identified during the conduct of the study. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of participants or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

10 RESULTS

10.1 Participants

A flowchart was developed for eligible participants enrollment based on study procedure in the protocol (Figure 1).

A total of 1024 participants were admitted to the selected hospitals and started receiving treatment of PIFELTRO™ or DELSTRIGO™ until September 30th, 2023. A total of 370 participants were screened for this study, and 358 participants were enrolled. Twelve participants were excluded for resistance to NNRTIs and other drugs included in ART prior to initiation of PIFELTRO™ or DELSTRIGO™. The screening and enrollment status of each site is shown in Table 1.

Of the 358 enrolled participants, six participants were removed from study population after it was discovered they had pre-existing resistance to NNRTIs prior to initiation of PIFELTRO™ or DELSTRIGO™ (protocol deviations) shown in Table 2. A total of 352 participants were finally included in the study population.

Of the 352 participants included in study population, 271 (77.0%) participants with available data to confirm the achievement of VS were included in the effectiveness analysis population, and 81 (23%) participants were excluded from the effectiveness analysis population, 9 (2.6%) participants discontinued PIFELTRO™ or DELSTRIGO™, 68 (19.3%) participants missed VL testing result at 48 ± 8 weeks, and 4 (1.1%) participants had the VL of the lower limit of detection > 50 copies/mL at week 48±8, as shown in Table 3 and Table 4.

Figure 1 Procedures of Eligible Participants Enrollment

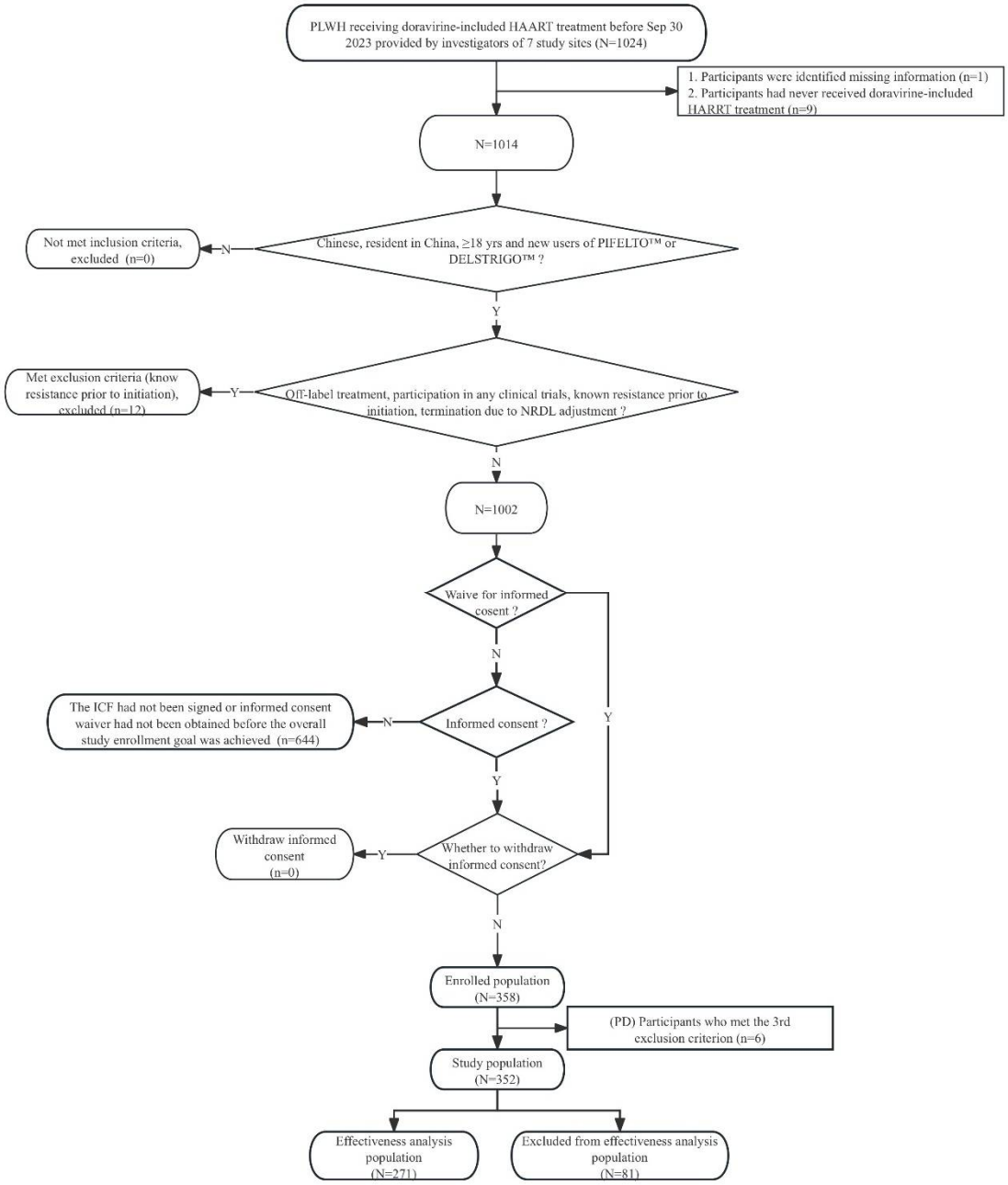

Table 1 Characteristics of Screened Population

Items	Public Health Clinical Center of Chengdu N=63	Guiyang Public Health Clinical Center N=99	Kunming Third People's Hospital N=40	Shanghai Public Health Clinical Center N=42	Beijing Ditan Hospital, Capital Medical University N=5	Beijing Youan Hospital, Capital Medical University N=32	Yunnan Provincial Hospital of Infectious Disease N=89	Total N=370
Participants screened, n	63	99	40	42	5	32	89	370
Non-enrolled participants, n(%)	0	0	0	4(9.5)	0	8(25.0)	0	12(3.2)
Enrolled participants, n(%)	63(100.0)	99(100.0)	40(100.0)	38(90.5)	5(100.0)	24(75.0)	89(100.0)	358(96.8)
Summary of reasons for non-enrollment, n(%)								
Meet the exclusion criteria	0	0	0	4(100.0)	0	8(100.0)	0	12(100.0)
Does not meet the inclusion criteria	0	0	0	0	0	0	0	0
Subject revoked the informed consent	0	0	0	0	0	0	0	0
Others	0	0	0	0	0	0	0	0

Abbreviations: N=number of participants in the population; n=number of participants in the specific category.
Note: The denominator (N) of the participants screened is the number of screened populations in each site or total, and the denominator of the summary of reasons for non-enrollment is the number of non-enrolled participants in each site or total.

Table 2 Protocol Deviations (Participants Enrolled)

Category	Total N=358 n(%)
Number of participants with at least one protocol deviation	15(4.2)
Improper AE/PQC/SAR reporting	9(60.0)
Not meeting I/E	6(40.0)
Inappropriate to obtain Informed Consent	0
Others	0

Note: Participants enrolled: the participants signed the ICF or were waived for informed consent and met the study inclusion/exclusion criteria after evaluation. In the Key Information for Enrollment section of the CRF, select "Yes" for "Whether the subject is enrolled?".
For the percentage of participants with at least one protocol deviation, the denominator (N) is the number of participants enrolled.
The denominator for each protocol deviation category is the number of participants with at least one protocol deviation. One participant may be counted in more than one protocol deviation category.

Table 3 Analysis Datasets

Site	Effectiveness analysis population N=271 n(%)	Excluded from the effectiveness analysis population N=81 n(%)	Study population N=352 n(%)
Public Health Clinical Center of Chengdu	58(21.4)	4(4.9)	62(17.6)
Guiyang Public Health Clinical Center	74(27.3)	21(25.9)	95(27.0)
Kunming Third People's Hospital	24(8.9)	16(19.8)	40(11.4)
Shanghai Public Health Clinical Center	31(11.4)	6(7.4)	37(10.5)
Beijing Ditan Hospital, Capital Medical University	0	5(6.2)	5(1.4)
Beijing Youan Hospital, Capital Medical University	20(7.4)	4(4.9)	24(6.8)
Yunnan Provincial Hospital of Infectious Disease	64(23.6)	25(30.9)	89(25.3)
Total	271(100.0)	81(100.0)	352(100.0)

Note: The denominator (N) for each site is the number of participants in the effectiveness population, excluded from the effectiveness population, or study population, respectively.

Table 4 Reasons for Exclusion from the Effectiveness Analysis Population

Items	Total N=352 n(%)
Without VL testing result at 48 ± 8 weeks	73*(20.7)
PIFELTRO™ or DELSTRIGO™ discontinuation	9*(2.6)
Participants who have VL, but the lower limit of detection is > 50 copies/mL at week 48±8	4(1.1)
Others	0

Note: The denominator (N) is the number of participants in the study population.
*A total of 5 participants were classified as either "Without VL testing result at 48 ± 8 weeks" or "PIFELTRO™ or DELSTRIGO™ discontinuation" and were recorded once in each of the corresponding items in this table.

10.1.1 Protection of Human Subjects

This is a non-interventional study, the study protocol and informed consent were submitted for review and approval by an IRB/ERC prior to study execution. The privacy of all participants was well protected, personal identification data was de-identified at the time of analysis, including but not limited to name and ID etc.

All demographic and diagnosis information for each eligible participant, as well as laboratory information were generated during the routine clinical practice and before the conduct of the retrospective chart review process. The information was tracked, collected, stored and used by selected hospitals or the study staff of the retrospective study and was not provided to entities outside the study.

IRB/ERC of six sites had approved the exemption of informed consent from participants under certain conditions, with the exception of the Chengdu Public Health Center. Overall, 8 participants from 3 sites (5 from Beijing You An, 2 from Shanghai, 1 from Guiyang) met the criteria for informed consent exemption and were included in the study without informed consent. Data from other participants were collected after obtaining their signed informed consent.

10.2 Descriptive data

The baseline characteristics of the study population are shown in Table 5. Among 352 study population, the mean age at baseline was 40.0 years. Higher proportion of the study population were male (84.9%), from west region (78.7%), paid by public medical insurance (66.8%) and paid by insurance covering DELSTRIGO™ (87.8%). Smoking status was collected for 116 participants, 9.1% participants (32/352) were current smokers. Drinking status was collected for 63 participants, among which 12.2% participants were (43/352) current drinkers. Among 53 participants with available pregnancy and lactation status, two women were pregnant within 1 year prior to index date and confirmed being not pregnant on index date. Eighty ART experienced participants were reported the VL within 30 days prior

to the index date, containing a high proportion of VL <50 copies/mL (92.5%), followed by VL ≥50 and ≤400 copies/mL (3.8%) and VL >400 copies/mL (3.8%). Sixty-four ART naïve participants were reported the VL within 30 days prior to the index date, containing a high proportion of VL <100,000 copies /mL (79.7%), followed by VL ≥100,000 copies/mL (20.3%).

Table 5 Demographic Characteristics (Study Population)

Parameter	Statistic	Study population N=352
Demographic characteristics		
Age (years)		
	n (Missing)	352(0)
	Mean (SD)	40.0(10.91)
	Median (Q1-Q3)	37.5(32.0-48.0)
	Min - Max	20-73
Gender, n(%)		
	n	352
	Male	299(84.9)
	Female	53(15.1)
	Others	0
Height (cm)		
	n (Missing)	291(61)
	Mean (SD)	170.2(7.12)
	Median (Q1-Q3)	171.0(167.0-175.0)
	Min - Max	150-188
Weight (kg)		
	n (Missing)	328(24)
	Mean (SD)	66.07(10.676)
	Median (Q1-Q3)	65.00(59.00-73.00)
	Min - Max	40.0-110.0
Smoking, n(%)		
	n	352
	Never smoke	77(21.9)
	Ex-smoker	7(2.0)

Parameter	Statistic	Study population N=352
	Current smoker	32(9.1)
	Unknown	236(67.0)
Alcohol use, n(%)		
	n	352
	Never	13(3.7)
	Ever	7(2.0)
	Currently	43(12.2)
	Unknown	289(82.1)
Geographic region, n(%)		
	n	352
	East	64(18.2)
	Central	8(2.3)
	West	277(78.7)
	Northeast	3(0.9)
Type of medical insurance, n(%)		
	n	352
	Public medical insurance	235(66.8)
	Commercial medical insurance	55(15.6)
	Self-pay	58(16.5)
	Others	4(1.1)
Insurance coverage for PIFELTRO™ or DELSTRIGO™, n(%)		
	n	352
	Yes[a]	309(87.8)
	No	18(5.1)
	Unknown	25(7.1)
Diagnosis history		
Pregnancy, n(%)		
	n (Female)	53
	Yes[b]	2(3.8)
	No	51(96.2)
Breast-feeding, n(%)		

Parameter	Statistic	Study population N=352
	n (Female)	53
	Yes	0
	No	39(73.6)
	Unknown	14(26.4)
VL within 30 days prior to index date		
ART naïve participant, n(%)		
	Missing (cannot be classified into the following two categories)	6
	n (include the following two categories)	64
	<100,000 copies/mL	51(79.7)
	≥100,000 copies/mL	13(20.3)
ART experienced participant, n(%)		
	Missing (cannot be classified into the following three categories)	202*
	n (include the following three categories)	80
	<50 copies/mL	74(92.5)
	≥50 and ≤400 copies/mL	3(3.8)
	>400 copies/mL	3(3.8)

Abbreviations: Missing=number of participants with missing data and show missing when number of missing > 0.
Note: For the percentages of all the variables, the denominator (n) is the number of participants with available data in study population.
*The baseline VL test results of 10 people were the following qualitative results: <100 copies/mL.
[a]It indicates that PIFELTRO™/DELSTRIGO™ have been covered by medical insurance during the participant's medication process, but it doesn't mean that the participant has the corresponding medical insurance.
[b]It indicates that the participant was pregnant within 12 months prior to index date but wasn't pregnant on index date.

There were 70 ART naïve participants and 282 experienced participants in the study population. The mean age of the naïve participants was 37.1 years, compared to 40.7 years in experienced participants in the study population (p=0.002). The proportion of males was very similar in the ART naïve participants (87.1%) and the ART experienced participants (84.4%) (p=0.565). No significant difference of *p*roportions in height, weight, smoking, drinking, geographic region and insurance covering DELSTRIGO™ between the ART naïve and the ART experienced participants (Table 6).

Table 6 Demographic Characteristics of ART naïve and experienced participants (Study Population)

Parameter	Statistic	ART naïve participants N=70	ART experienced participants N=282	P-value
Demographic characteristics				
Age (years)				0.002
	n(Missing)	70(0)	282(0)	
	Mean (SD)	37.1(12.34)	40.7(10.43)	
	Median (Q1-Q3)	33.0(28.0-44.5)	39.0(33.0-48.8)	
	Min - Max	20-69	21-73	
Gender, n(%)				0.565
	n	70	282	
	Male	61(87.1)	238(84.4)	
	Female	9(12.9)	44(15.6)	
	Others	0	0	
Height (cm)				0.223
	n(Missing)	68(2)	223(59)	
	Mean (SD)	169.1(7.29)	170.5(7.05)	
	Median (Q1-Q3)	170.0(164.8-174.3)	171.0(167.0-175.0)	
	Min - Max	150-183	150-188	
Weight (kg)				0.685
	n(Missing)	68(2)	260(22)	
	Mean (SD)	65.50(11.410)	66.22(10.494)	
	Median (Q1-Q3)	65.00(59.75-70.00)	65.00(59.00-75.00)	
	Min - Max	40.0-110.0	42.0-104.0	
Smoking, n(%)				0.849
	n	70	282	
	Never smoke	14(20.0)	63(22.3)	
	Ex-smoker	1(1.4)	6(2.1)	
	Current smoker	8(11.4)	24(8.5)	
	Unknown	47(67.1)	189(67.0)	
Alcohol use, n(%)				0.526
	n	70	282	
	Never	2(2.9)	11(3.9)	
	Ever	0	7(2.5)	

Parameter	Statistic	ART naïve participants N=70	ART experienced participants N=282	P-value
	Currently	11(15.7)	32(11.3)	
	Unknown	57(81.4)	232(82.3)	
Geographic region, n(%)				0.423
	n	70	282	
	East	9(12.9)	55(19.5)	
	Central	1(1.4)	7(2.5)	
	West	59(84.3)	218(77.3)	
	Northeast	1(1.4)	2(0.7)	
Type of medical insurance, n(%)				<0.001
	n	70	282	
	Public medical insurance	41(58.6)	194(68.8)	
	Commercial medical insurance	0	55(19.5)	
	Self-pay	29(41.4)	29(10.3)	
	Others	0	4(1.4)	
Insurance coverage for PIFELTRO™ or DELSTRIGO™, n(%)				0.644
	n	70	282	
	Yes[a]	60(85.7)	249(88.3)	
	No	5(7.1)	13(4.6)	
	Unknown	5(7.1)	20(7.1)	
Diagnosis history				
Pregnancy, n(%)				1.000
	n (Female)	9	44	
	Yes[b]	0	2(4.5)	
	No	9(100.0)	42(95.5)	
Breast-feeding, n(%)				0.416
	n (Female)	9	44	
	Yes	0	0	
	No	8(88.9)	31(70.5)	
	Unknown	1(11.1)	13(29.5)	
VL within 30 days prior to index date				

Parameter	Statistic	ART naïve participants N=70	ART experienced participants N=282	P-value
ART naïve participant n(%)				-
	Missing (cannot be classified into the following two categories)	6	-	
	n (include the following two categories)	64	-	
	<100,000 copies/mL	51(79.7)	-	
	≥100,000 copies/mL	13(20.3)	-	
ART experienced participant, n(%)				-
	Missing (cannot be classified into the following three categories)	-	202*	
	n (include the following three categories)	-	80	
	<50 copies/mL	-	74(92.5)	
	≥50 and ≤400 copies/mL	-	3(3.8)	
	>400 copies/mL	-	3(3.8)	

Note: For the percentages of all the variables, the denominator (n) is the number of participants with available data in ART naïve participants or ART experienced participants, respectively.
P-value: Comparison between ART naïve and experienced participants of the study population.
*The baseline VL test results of 10 people were as follows: <100 copies/mL.
[a]It indicates that PIFELTRO™/DELSTRIGO™ have been covered by medical insurance during the participant's medication process, but it doesn't mean that the participant has the corresponding medical insurance.
[b]It indicates that the participant was pregnant within 12 months prior to index date but wasn't pregnant on index date.

The demographic and clinical characteristics between participants included and excluded from the effectiveness analysis population were presented in Table 7. The mean age, mean height and mean weight were similar between the two groups. The proportions of males, smoking, drinking, geographic region, paid by basic medical insurance and paid by insurance covering DELSTRIGO™, pregnancy and lactation were similar in the two groups. Compared to ART naïve participants excluded from the effectiveness analysis population, higher proportion of VL <100,000 copies /mL within 30 days prior to the index date in ART naïve participants included in the effectiveness analysis population (42.9% vs. 84.2%, p=0.027), based on 7 participants excluded from the effectiveness analysis population and 57 participants included in the effectiveness analysis population. No significant difference observed in the VL within 30 days prior to the index date for ART experienced participants between the participants included and excluded from the effectiveness analysis population (p=1.000).

Table 7 Demographic and Clinical Characteristics of Participants Included and Excluded from the Effectiveness Analysis Population

Parameter	Statistic	Effectiveness analysis population N=271	Excluded from the effectiveness analysis population N=81	P-value
Demographic characteristics				
Age (years)				0.464
	n (Missing)	271(0)	81(0)	
	Mean (SD)	39.8(10.97)	40.6(10.77)	
	Median (Q1-Q3)	37.0(31.5-47.0)	39.0(33.0-49.0)	
	Min - Max	20-73	22-68	
Gender, n(%)				0.523
	n	271	81	
	Male	232(85.6)	67(82.7)	
	Female	39(14.4)	14(17.3)	
	Others	0	0	
Height (cm)				0.544
	n (Missing)	235(36)	56(25)	
	Mean (SD)	170.0(7.34)	171.0(6.11)	
	Median (Q1-Q3)	170.0(165.0-175.0)	171.5(168.0-175.0)	
	Min - Max	150-188	156-185	
Weight (kg)				0.731
	n (Missing)	255(16)	73(8)	
	Mean (SD)	65.87(10.244)	66.78(12.115)	
	Median (Q1-Q3)	65.00(59.00-73.00)	65.00(60.00-75.00)	
	Min - Max	40.0-95.0	46.0-110.0	
Smoking, n(%)				0.401
	n	271	81	
	Never smoke	54(19.9)	23(28.4)	

Parameter	Statistic	Effectiveness analysis population N=271	Excluded from the effectiveness analysis population N=81	P-value
	Ex-smoker	5(1.8)	2(2.5)	
	Current smoker	26(9.6)	6(7.4)	
	Unknown	186(68.6)	50(61.7)	
Alcohol use, n(%)				0.803
	n	271	81	
	Never	9(3.3)	4(4.9)	
	Ever	5(1.8)	2(2.5)	
	Currently	33(12.2)	10(12.3)	
	Unknown	224(82.7)	65(80.2)	
Geographic region, n(%)				0.145
	n	271	81	
	East	52(19.2)	12(14.8)	
	Central	5(1.8)	3(3.7)	
	West	213(78.6)	64(79.0)	
	Northeast	1(0.4)	2(2.5)	
Type of medical insurance, n(%)				0.582
	n	271	81	
	Public medical insurance	182(67.2)	53(65.4)	
	Commercial medical insurance	39(14.4)	16(19.8)	
	Self-pay	47(17.3)	11(13.6)	
	Others	3(1.1)	1(1.2)	
Insurance coverage for PIFELTRO™ or DELSTRIGO™, n(%)				0.423
	n	271	81	
	Yes[a]	235(86.7)	74(91.4)	

Parameter	Statistic	Effectiveness analysis population N=271	Excluded from the effectiveness analysis population N=81	P-value
	No	16(5.9)	2(2.5)	
	Unknown	20(7.4)	5(6.2)	
Diagnosis history				
Pregnancy, n(%)				0.462
	n (Female)	39	14	
	Yes[b]	1(2.6)	1(7.1)	
	No	38(97.4)	13(92.9)	
Breast-feeding, n(%)				0.305
	n (Female)	39	14	
	Yes	0	0	
	No	27(69.2)	12(85.7)	
	Unknown	12(30.8)	2(14.3)	
VL within 30 days prior to index date				
ART naïve participant, n(%)				0.027
	Missing (cannot be classified into the following two categories)	3	3	
	n (include the following two categories)	57	7	
	<100,000 copies/mL	48(84.2)	3(42.9)	
	≥100,000 copies/mL	9(15.8)	4(57.1)	
ART experienced participant, n(%)				1.000
	Missing (cannot be classified into the following three categories)	139[*]	63[**]	
	n (include the following three categories)	72	8	

Parameter	Statistic	Effectiveness analysis population N=271	Excluded from the effectiveness analysis population N=81	P-value
	<50 copies/mL	66(91.7)	8(100.0)	
	≥50 and ≤400 copies/mL	3(4.2)	0	
	>400 copies/mL	3(4.2)	0	

Note: For the percentages of all the variables, the denominator (n) is the number of participants with available data in the effectiveness analysis population, or the population excluded from the effectiveness population, respectively.
P-value: Comparison between participants included and excluded from the effectiveness analysis population.
*The baseline VL test results of 4 people were as follows: <100 copies/mL.
**The baseline VL test results of 6 people were as follows: <100 copies/mL.
[a]It indicates that PIFELTRO™/DELSTRIGO™ have been covered by medical insurance during the participant's medication process, but it doesn't mean that the participant has the corresponding medical insurance.
[b]It indicates that the participant was pregnant within 12 months prior to index date but wasn't pregnant on index date.

There were 60 ART naïve participants and 211 experienced participants in the effectiveness analysis population. The mean age of the ART naïve participants was 37.4 years, compared to 40.5 years in ART experienced participants (p=0.002). The proportion of males was very similar in the ART naïve participants (86.7%) and the ART experienced participants (85.3%) (p=0.791). No significant difference of proportions in height, weight, smoking, drinking, geographic region and insurance covering DELSTRIGO™ between the ART naïve and the ART experienced participants. Seventy-two ART experienced participants were reported the VL within 30 days prior to the index date, containing a high proportion of VL <50 copies/mL (91.7%), followed by VL ≥ 50 and ≤400 copies/mL (4.2%) and VL >400 copies/mL (4.2%). Fifth-seven ART naïve participants were reported theVL within 30 days prior to the index date, containing a high proportion of VL <100,000 copies /mL (84.2%), followed by VL ≥100,000 copies/mL (15.8%) (Table 8).

Table 8 Demographic and Clinical Characteristics of ART naïve and experienced participants (Effectiveness Analysis Population)

Parameter	Statistic	ART naïve participants N=60	ART experienced participants N=211	P-value
Demographic characteristics				
Age (years)				0.002
	n(Missing)	60(0)	211(0)	
	Mean (SD)	37.4(12.53)	40.5(10.41)	

Parameter	Statistic	ART naïve participants N=60	ART experienced participants N=211	P-value
	Median (Q1-Q3)	33.0(28.0-43.5)	38.0(32.0-48.0)	
	Min - Max	20-69	21-73	
Gender, n(%)				0.791
	n	60	211	
	Male	52(86.7)	180(85.3)	
	Female	8(13.3)	31(14.7)	
	Others	0	0	
Height (cm)				0.229
	n(Missing)	58(2)	177(34)	
	Mean (SD)	169.0(7.50)	170.4(7.27)	
	Median (Q1-Q3)	170.0(164.3-174.0)	171.0(167.0-175.0)	
	Min - Max	150-183	150-188	
Weight (kg)				0.667
	n (Missing)	59(1)	196(15)	
	Mean (SD)	64.85(10.130)	66.18(10.284)	
	Median (Q1-Q3)	65.00(59.50-70.00)	65.00(58.75-75.00)	
	Min - Max	40.0-85.0	42.0-95.0	
Smoking, n(%)				0.934
	n	60	211	
	Never smoke	10(16.7)	44(20.9)	
	Ex-smoker	1(1.7)	4(1.9)	
	Current smoker	6(10.0)	20(9.5)	
	Unknown	43(71.7)	143(67.8)	
Alcohol use, n(%)				0.689
	n	60	211	
	Never	2(3.3)	7(3.3)	
	Ever	0	5(2.4)	

Parameter	Statistic	ART naïve participants N=60	ART experienced participants N=211	P-value
	Currently	9(15.0)	24(11.4)	
	Unknown	49(81.7)	175(82.9)	
Geographic region, n(%)				0.337
	n	60	211	
	East	7(11.7)	45(21.3)	
	Central	1(1.7)	4(1.9)	
	West	52(86.7)	161(76.3)	
	Northeast	0	1(0.5)	
Type of medical insurance, n(%)				<0.001
	n	60	211	
	Public medical insurance	35(58.3)	147(69.7)	
	Commercial medical insurance	0	39(18.5)	
	Self-pay	25(41.7)	22(10.4)	
	Others	0	3(1.4)	
Insurance coverage for PIFELTRO™ or DELSTRIGO™, n(%)				0.491
	n	60	211	
	Yes[a]	52(86.7)	183(86.7)	
	No	5(8.3)	11(5.2)	
	Unknown	3(5.0)	17(8.1)	
Diagnosis history				
Pregnancy, n(%)				1.000
	n (Female)	8	31	
	Yes[b]	0	1(3.2)	
	No	8(100.0)	30(96.8)	

Parameter	Statistic	ART naïve participants N=60	ART experienced participants N=211	P-value
Breast-feeding, n(%)				0.394
	n (Female)	8	31	
	Yes	0	0	
	No	7(87.5)	20(64.5)	
	Unknown	1(12.5)	11(35.5)	
VL within 30 days prior to index date				
ART naïve participants, n(%)				-
	Missing (cannot be classified into the following two categories)	3	-	
	n (include the following two categories)	57	-	
	<100,000 copies/mL	48(84.2)	-	
	≥100,000 copies/mL	9(15.8)	-	
ART experienced participants, n(%)				-
	Missing (cannot be classified into the following three categories)	-	139*	
	n (include the following three categories)	-	72	
	<50 copies/mL	-	66(91.7)	
	≥50 and ≤400 copies/mL	-	3(4.2)	
	>400 copies/mL	-	3(4.2)	

Note: For the percentages of all the variables, the denominator (n) is the number of the participants with available data in ART naïve participants and ART experienced participants, respectively.
P-value: Comparison between ART naïve and experienced participants of the effectiveness analysis population.
*The baseline VL test results of 4 people were as follows: <100 copies/mL.
[a]It indicates that PIFELTRO™/DELSTRIGO™ have been covered by medical insurance during the participant's medication process, but it doesn't mean that the participant has the corresponding medical insurance.
[b]It indicates that the participant was pregnant within 12 months prior to index date but wasn't pregnant on index date.

10.3 Outcome data

Virologic suppression at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration in the effectiveness analysis population

A total of 271 participants with available data to confirm the achievement of VS were identified in the effectiveness analysis population. A total of 254 participants achieved VS among 271 participants at week 48±8, and 17 participants didn't achieve VS. Among the 17 participants without VS, 14 participants were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant was confirmed to have VL >200 copies/mL (285 copies/mL), and 2 participants were confirmed to have VL >1000 copies/mL (26,500 copies/mL and 19,959 copies/mL) at week 48±8 likely due to low adherence rates (54%-64%). No virologic failure before week 40 was confirmed since no documents in EMR/paper medical records have been found (Table 9).

Virologic suppression at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration in the participants with adherence ≥80%

Adherence could be calculated in 248 participants with available prescription information to confirm adherence ≥80% during the period of 48±8 weeks. A total of 233 participants achieved VS at week 48±8, and 15 participants didn't achieve VS. Among the 15 participants without VS at week 48±8, 14 participants were confirmed to have VL between 50 copies/mL and 200 copies/mL, and 1 participant was confirmed to have VL >200 copies/mL (285 copies/mL). No virologic failure before week 40 was confirmed (Table 10).

Virologic suppression at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration in ART naïve participants vs. ART experienced participants with or without virologic suppression before DOR initiation

At baseline there are 60 ART naïve participants and 211 ART experienced participants with or without VS. At week 48±8, 54 ART naïve participants and 200 ART experienced participants achieved VS, respectively. Of 6 ART naïve participants without achieving VS at week 48±8, all the participants had no genotypic drug resistance testing at baseline, and 2 participants were found to be resistant to NNRTI class (EFV and NVP) after 6 months of doravirine-containing treatment (probably due to pre-existing primary resistance-associated mutations to NNRTI). Of 11 experienced participants without achieving VS at week 48±8, 6 participants (54.5%) had no drug resistance testing and unknown VL at baseline (including 1 participant with low adherence rate of 54%), 3 participants (27.3%) had no drug resistance testing and confirmed a VS at baseline, and 1 participants (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and confirmed a VS at baseline, and 1 participants (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and unknown VL with adherence rate of 64% (Table 10).

Virologic suppression at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration in ART naïve participants and ART experienced participants without VS before DOR initiation vs. ART experienced participants with VS before DOR initiation

There were 66 participants who were ART naïve participants or ART experienced participants without VS before DOR initiation. At week 48±8, 60 ART naïve participants or ART experienced participants without virologic suppression before DOR initiation achieved VS. Only 66 experienced participants can be confirmed VS before DOR initiation, of which 62 participants achieved VS at week 48±8 (Table 10).

10.4 Main results

10.4.1 Proportion of participants with VS at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration

As shown in Table 9, a total of 254 participants achieved VS among 271 participants at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration, and the proportion of VS was 93.7% (95% CI: 90.8%, 96.6%). Only 17 participants didn't achieve VS at week 48±8, of whom 14 participants (82.4%) were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant (5.8%) was confirmed to have VL >200 copies/mL (285 copies/mL), and 2 participants (11.8%) were confirmed to have VL >1000 copies/mL (19,959 and 26,500 copies/mL) at week 48±8 likely due to low adherence rates (54%-64%).

Among 248 participants with adherence ≥80% during the period of 48±8 weeks, the proportion of VS was 94.0% (95% CI: 91.0%, 96.9%). Only 15 participants didn't achieve VS at week 48±8, of whom 14 participants (93.3%) were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant (6.7%) was confirmed to have VL >200 copies/mL (285 copies/mL) (Table 10).

Among 60 ART naïve participants and 211 ART experienced participants regardless of VS at baseline, 90.0% (95% CI: 82.4%, 97.6%) of ART naïve participants and 94.8% (95% CI: 91.8%, 97.8%) of ART experienced participants achieved VS at week 48±8, respectively. Of 6 naïve participants without achieving VS at week 48±8, all the participants had no genotypic drug resistance testing at baseline, and 2 participants were found to be resistant to NNRTI class (EFV and NVP) after 6 months of doravirine-containing treatment (probably due to pre-existing primary resistance-associated mutations to NNRTI). Of 11 experienced participants without achieving VS at week 48±8, 6 participants (54.5%) had no drug resistance testing and unknown VL at baseline (including 1 participant with low adherence rate of 54%), 3 participants (27.3%) had no drug resistance testing and confirmed a VS at baseline, and 1 participant (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and confirmed a VS at baseline, and 1 participant (9.1%) had drug resistance testing at baseline without resistance to NNRTI class and unknown VL with adherence rate of 64%. There was no significant difference in the proportion of VS between the ART naïve and the ART experienced participants (p=0.224, Table 10).

Among 66 participants who were ART naïve participants or ART experienced participants without VS before DOR initiation, 90.9% (95% CI: 84.0%, 97.8%) achieved VS at week 48±8. Among 66 experienced participants who could be confirmed VS before DOR initiation, 93.9% (95% CI: 88.2%, 99.7%) achieved VS at week 48±8. No significant difference in the proportion of VS between the two sub-groups (p=0.551, Table 10).

Table 9 Primary Endpoint Analysis (Effectiveness Analysis Population)

Viral load	Effectiveness analysis population N=271 n(%)	95% CI*
<50 copies/mL	254(93.7)	90.8, 96.6
≥50copies/mL	17(6.3)	3.4, 9.2
≥50copies/mL and ≤400copies/mL	15(5.5)	2.8, 8.3
>400copies/mL	2(0.7)	0.0, 1.8
Virologic failure	0	-
Total	271(100.0)	-

Note: The denominator (N) is the number of the effectiveness analysis population.
*A 95% CI for a binomial proportion were estimated using the Wald's (Normal Approximation) method.
Though virologic failure is defined as continuous plasma VL of >200 copies/mL after 24 weeks of treatment, or detectable VL of ≥200 copies/mL after achieving virologic suppression according to the Chinese guideline of diagnosis and treatment of HIV/AID (2021 edition), the virologic failure is designated by investigators and documented in EMR/paper medical records in the study.

Table 10 Subgroup Analysis of Primary Endpoint (Effectiveness Analysis Population)

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	95% CI	P-value
VL for adherence ≥80%				-
	n	248	-	
	<50 copies/mL	233(94.0)	91.0, 96.9	
	≥50copies/mL	15(6.0)	3.1, 9.0	
	≥50 copies/mL and ≤400 copies/mL	15(6.0)	3.1, 9.0	
	>400 copies/mL	0	-	
	Virologic failure	0	-	

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	95% CI	P-value
VL for ART naïve participants				0.224[a]
	n	60	-	
	<50 copies/mL	54(90.0)	82.4, 97.6	
	≥50copies/mL	6(10.0)	2.4, 17.6	
	Virologic failure	0	-	
VL for ART experienced participants				-
	n	211	-	
	<50 copies/mL	200(94.8)	91.8, 97.8	
	≥50copies/mL	11(5.2)	2.2, 8.2	
	Virologic failure	0	-	
VL for ART naïve and ART experienced participants without virologic suppression group before DOR initiation				0.511[b]
	n	66	-	
	<50 copies/mL	60(90.9)	84.0, 97.8	
	≥50copies/mL	6(9.1)	2.2, 16.0	
	Virologic failure	0	-	
VL for ART-experienced participants with virologic suppression group before DOR initiation				-
	n	66	-	
	<50 copies/mL	62(93.9)	88.2, 99.7	

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	95% CI	P-value
	≥50copies/mL	4(6.1)	0.3, 11.8	
	Virologic failure	0	-	

Note: There are two p-value: a. comparison of the proportions of the VL <50 copies/mL between the ART naïve and ART experienced participants; b. comparison of the proportions of the VL which is <50 copies/mL between the ART naïve and ART experienced participants with and without virologic suppression group.
The denominator (n) is the number of participants in the specific category in the effectiveness analysis population.

10.4.2 Sensitivity analysis for proportion of participants with VS at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration

Sensitivity analysis 1:

Assuming that only the last available virologic result for a participant with multiple virologic results at week 48±8 is used for VS estimation, this approach aligns most closely with the FDA guidance for VS estimation. Four participants underwent two HIV-1 RNA tests at week 48±8, of whom only one had two different test results: one result, taken closest to the 48-week point, was 64.3 copies/mL, while the other was the last available measurement result at week 48±8, which was a target not detected (TND). The other 3 participants had the same test results showing "TND", which indicated the results were lower than LLOD of 50 copies/mL. As shown in the sensitivity analysis 1, which used the last available virologic result for a participant with multiple virologic results at week 48±8 (Table 11), 255 (94.1%, 95% CI: 91.3%, 96.9%) of 271 participants achieved VS. Only 16 participants didn't achieve VS at week 48±8, of whom 13 (81.3%) were confirmed to have VL between 50 copies/mL and 200 copies/mL, 1 participant (6.2%) was confirmed to have VL >200 copies/mL (285 copies/mL), and 2 participants (12.5%) were confirmed to have VL >19, 900 copies/mL (19,959 copies/mL and 26,500 copies/mL) at week 48±8. No virologic failure before week 40 was documented.

Table 11 Primary Endpoint Analysis (Effectiveness Analysis Population)-Sensitivity analysis 1

Viral load	Effectiveness analysis population N=271 n(%)	95% CI*
<50 copies/mL	255(94.1)	91.3, 96.9
≥50copies/mL	16(5.9)	3.1, 8.7
≥50copies/mL and ≤400copies/mL	14(5.2)	2.5, 7.8
>400copies/mL	2(0.7)	0.0, 1.8
Virologic failure	0	-
Total	271(100.0)	-

Note: The denominator (N) is the number of the effectiveness analysis population.
*A 95% CI for a binomial proportion were estimated using the Wald's (Normal Approximation) method. Though virologic failure is defined as continuous plasma VL of >200 copies/mL after 24 weeks of treatment, or detectable VL of ≥200 copies/mL after achieving VS according to the Chinese guideline of diagnosis and treatment of HIV/AID (2021 edition), the virologic failure is designated by investigators and documented in EMR/paper medical records in the study. HIV virologic information was determined by the last available measurement while the participant is on treatment within week 48±8.

Sensitivity analysis 2:

There were rare ART-experienced participants with VL <100 copies/mL at baseline because the detection limit at baseline was 100 copies/mL instead of 50 copies/mL and thus can't be stratified as participants with VS or not at baseline given that VS was defined as VL <50 copies/mL. The subgroup analysis related to participants with VS or without VS before DOR initiation would therefore not include these participants per the protocol. In sensitivity analysis 2, participants for whom an assay with an LLOD of 100 copies/mL was used and who had a VL of less than 100 copies/mL at baseline were included (indicating VS before DOR initiation). However, those for whom an assay with an LLOD of 50 copies/mL was used and who had a VL between 51 and 99 copies/mL were excluded. Among the 70 ART-experienced participants who could be confirmed as having VS before the initiation of DOR, 94.3% (95% CI: 88.8%, 99.7%) achieved VS at week 48±8. No significant difference in the proportion of VS between the two subgroups (ART naïve participants and ART experienced participants without VS before DOR initiation vs. ART experienced participants with VS before DOR initiation) was observed based on the sensitivity analysis (p=0.523, Table 12).

Sensitivity analysis 3:

In sensitivity analysis 3, which used the adherence cutoff of at least 95% (Table 12), 204 out of 217 participants (94.0%, 95% CI: 90.9%, 97.2%) achieved VS. The remaining 12 participants were confirmed to have a VL between 50 copies/mL and 200 copies/mL and 1 participant was confirmed to have VL >200 copies/mL (285 copies/mL). No participants with adherence ≥95% had a VL >400 copies/mL at week 48±8. The proportion of participants with adherence ≥95% achieving VS was similar to those with adherence ≥80% at week 48±8.

Table 12 Subgroup Analysis of Primary Endpoint (Effectiveness Analysis Population) - Sensitivity analysis 2 and 3

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	95% CI	P-value
VL for adherence ≥95%				-
	n	217	-	
	<50 copies/mL	204(94.0)	90.9, 97.2	
	≥50copies/mL	13(6.0)	2.8, 9.1	
	≥50 copies/mL and ≤400 copies/mL	13(6.0)	2.8, 9.1	
	>400 copies/mL	0	-	
	Virologic failure	0	-	
VL for ART naïve and ART experienced participants without virologic suppression group before DOR initiation				0.523[a]
	n	66	-	
	<50 copies/mL	60(90.9)	84.0, 97.8	
	≥50copies/mL	6(9.1)	2.2, 16.0	
	Virologic failure	0	-	
VL for ART-experienced participants with virologic suppression group before DOR initiation[*]				-
	n	70	-	
	<50 copies/mL	66(94.3)	88.8, 99.7	
	≥50copies/mL	4(5.7)	0.3, 11.2	

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	95% CI	P-value
	Virologic failure	0	-	

Note: The denominator (n) is the number of participants in the specific category in the effectiveness analysis population.
*Participants with VS before DOR initiation include participants for whom an assay with the lower limit of detection of 100 copies/mL was used and who had VL <100 copies/mL at baseline, but would exclude someone for whom an assay with the lower limit of detection of 50 copies/mL was used and who had a VL between 51 and 99 copies/mL.
[a]comparison of the proportions of the VL which is <50 copies/mL between the ART naïve and ART experienced participants with and without virologic suppression group.

10.4.3 Clinical characteristics and treatment patterns

The clinical characteristics of the study population are shown in Table 13. Among 349 participants with available comorbidities information during the observation period, 166 (47.6%) participants had at least one comorbid disease in the study population. In ART naïve participants and experienced participants, the proportions of participants with at least one comorbid disease were 40.6% and 49.3%, respectively (p=0.195). There was no significant difference of the proportions of all the comorbidities listed between ART-naïve and experienced participants. The most common comorbidities were cardiovascular and renal diseases (32.1% in study population, 26.1% in ART naïve participants, 33.6% in experienced participants) and liver diseases (25.5% in study population, 21.7% in ART naïve participants, 26.4% in experienced participants). The high incidence of renal and liver disease may be related to the adverse reactions of antiviral therapeutic drugs. However, it is unclear whether lipid metabolism-related adverse reactions already existed before the index date.

There were 53 female participants in the study population, including 9 ART naïve participants and 44 experienced participants. No female participants were pregnant or breast-feeding during the observation period. No deaths were found in the study period.

No concomitant medications were found since only concomitant medication that may interact with doravirine-containing treatment during the observation period had been extracted from EMR/paper medical record (not limited to strong cytochrome P450 (CYP)3A enzyme inducers, Table 14).

Table 13 Comorbidities and Diagnosis History During the Observation Period (Study Population)

Parameter	Statistic	ART naïve participants N=70 n(%)	ART experienced participants N=282 n(%)	Study population N=352 n(%)	P-value
Comorbid diseases					0.763
	Missing	1	2	3	-
	n	69	280	349	-
	Participants with at least one comorbid disease	28(40.6)	138(49.3)	166(47.6)	0.195
	Cardiovascular and Renal Diseases	18(26.1)	94(33.6)	112(32.1)	0.233
	Liver Diseases	15(21.7)	74(26.4)	89(25.5)	0.423
	Mental Health and Pain Conditions	2(2.9)	19(6.8)	21(6.0)	0.394
	Gastrointestinal Diseases	0	11(3.9)	11(3.2)	0.131
	Endocrine Disorders	1(1.4)	3(1.1)	4(1.1)	0.588
	Cancer, Non-AIDS and AIDS-Defining Cancers	0	2(0.7)	2(0.6)	1.000
	Autoimmune Diseases	0	2(0.7)	2(0.6)	1.000
	Pulmonary Diseases	0	1(0.4)	1(0.3)	1.000
Pregnancy					
	n (Female)	9	44	53	-
	Participants with at least one pregnancy	0	0	0	-
Breast-feeding					
	n (Female)	9	44	53	-
	Participants with at least one breast-feeding	0	0	0	-
Death					
	n	70	282	352	-

Parameter	Statistic	ART naïve participants N=70 n(%)	ART experienced participants N=282 n(%)	Study population N=352 n(%)	P-value
	Number of deaths	0	0	0	-

Note: For the percentages of all the variables, the denominator (n) is the number of participants with available data in ART naïve participants, ART experienced participants or the study population, respectively.
P-value: Comparison between ART naïve and experienced participants of the study population.

Table 14 Concomitant Medication During the Observation Period (Study Population)

Concomitant medication	Statistic	ART naïve participants N=70 n(%)	ART experienced participants N=282 n(%)	Study population N=352 n(%)	P-value
P450 (CYP)3A enzyme inducers					
	n	70	282	352	-
	Participants with at least one P450 (CYP)3A enzyme inducers	0	0	0	-
Indication					
	Anticonvulsants	0	0	0	-
	Androgen receptor inhibitor	0	0	0	-
	Antimycobacterials	0	0	0	-
	Cytotoxic agent	0	0	0	-
	St. John's wort	0	0	0	-
	Others	0	0	0	-

Note: Anticonvulsants include Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin; androgen receptor inhibitor includes enzalutamide; Antimycobacterials include rifampin, Rifapentine; cytotoxic agent includes Mitotane.
For the percentages of all the variables, the denominator (n) is the number of participants with available data in ART naïve participants, ART experienced participants or the study population, respectively.
P-value: Comparison between ART naïve and experienced participants of the study population.

All previous cART regimens within 1 year prior to index date in experienced participants were shown in Table 15. Among 282 ART experienced participants in the study population, the most common regimen within 1 year before the index date was dual NRTI+NNRTI (78.0%), followed by dual NRTI/1 NRTI+INSTI regimen (12.8%), dual NRTI+PI regimen

(7.8%) and others (1.4%). A total of 59 participants (20.9%) had at least one change in cART regimen during 1-year prior to index date. The cART regimen used in the effectiveness analysis population before the index date was similar to that of the study population.

Table 15 The cART Regimens During the 1-year Prior to Index Date

cART regimens	Effectiveness analysis population N=211* n(%)	Study population N=282* n(%)
n	211[a]	282[b]
Dual NRTI+NNRTI	171(81.0)	220(78.0)
Dual NRTI+PI	14(6.6)	22(7.8)
Dual NRTI/NRTI+INSTI	23(10.9)	36(12.8)
PI+INSTI	0	0
Others	3(1.4)	4(1.4)

Note: For the calculation of the corresponding variable proportion, the denominator (total) is the number of participants with the variable not missing in the effectiveness analysis population or the study population.
*Corresponds to ART experienced participants in the effectiveness analysis population or the study population, respectively.
[a]Among the ART experienced participants in the effectiveness analysis population, 44 participants (20.9%) had at least one change in cART regimen during the 1-year prior to index date.
[b]Among the ART experienced participants in the study population, 59 participants (20.9%) had at least one change in cART regimen during 1-year prior to index date.

A total of 42 (11.9%) participants had at least one resistance gene examination prior to index date among the study population. The following NNRTI mutation were identified in 2 out of 6 participants who had been excluded from the study population: V179E, E138K (other participants' mutation were not reported). Thus no participants were reported to be resistant to NNRTIs and other drugs included in ART before the index date in the study population (Table 16, Listing 1 and Listing 2 in Annex 3).

A total of 18 (5.1%) participants had at least one genotypic drug resistance testing during observation period among 352 study population, including 12 (17.1% of all ART naïve participants) naïve participants and 6 (2.1% of all ART experienced participants) experienced participants. The proportion of ART naïve participants who had drug resistance testing was higher than ART experienced participants with statistically significance (p<0.001) (Table 17).

Of the 18 participants, a total of 4 participants were found to have genotype-specific drug resistance during observation period, including 2 (16.7%) ART naïve and 2 (33.3%) ART experienced participants. The proportions of at least one drug resistance were comparable between ART naïve and ART experienced participants who had available drug resistance testing results (p=0.569). Of the 4 participants, 2 participants were resistant to NNRTIs, but no genotype mutations associated with DOR resistance were identified. One participant was resistant to PIs (nelfinavir [NFV], tipranavir/ritonavir [TPV/r]), and another participant was

resistant to NRTIs (stavudine [D4T], didanosine [DDI], abacavir [ABC], emtricitabine [FTC], 3TC, TDF). None of four participants discontinued PIFELTRO™ or DELSTRIGO™, and three of them had available VL at week 48±8. Specifically, the two participants with resistance to NNRTIs were both ART naïve participants and the genotypic drug resistance testing occurred after 24 weeks of treatment without achieving VS at the testing timepoint, which resulted in highly resistance to EFV and NVP. The two participants with resistance to NNRTIs did not achieve VS at week 48±8 (one VL was 110 copies/mL and another one was 540 copies/mL). The 2 participants with resistance to PIs and NRTIs received genotypic drug resistance testing within one week after the index date (it should be considered as genotypic drug resistance tests at baseline). The participant with resistance to PIs achieved VS (TND) at week 48±8 and the participant with resistance to NRTIs didn't have available virologic result at week 48±8 (Table 17; Listing 4, Listing 5 and Listing 6 in Annex 3).

Notably, among the other 14 participants without drug resistance, 10 participants received genotypic drug resistance testing within one week after the index date (it should be considered as genotypic drug resistance tests at baseline), 3 participants received drug resistance testing after 24 weeks of treatment given unsatisfactory decline in VL after 24 weeks (the HIV-1 RNA of these 3 participants were 144 copies/mL, 310 copies/mL and 142 copies/mL respectively). Another participant tested drug resistance had a VL of 248 copies/ml at 30 weeks of treatment, and the drug resistance testing was conducted at 35 weeks, but VL data at 35 weeks were not reported. Of the 10 participants who received drug resistance testing at baseline, 8 participants achieved VS at week 48±8, 1 participant didn't have available virologic data at week 48±8, and 1 participant had two VL testing results at week 48±8 (one was 64.3 copies/mL, another one was TND), which might be considered as a blips. Of the 4 participants who received drug resistance testing after 24 weeks, 2 participants didn't have available virologic data at week 48±8, 1 participant couldn't be regarded as VS or not for whom an assay with the LLOD of 250 copies/mL at week 48±8, and 1 participant achieved VS (<20 copies/mL) at week 48±8. This indicates that participants who had evidence of no drug resistance no matter at baseline or during the treatment process were likely to achieve satisfactory therapeutic effects after 48 weeks of treatment (Listing 3 and Listing 4 in Annex 3).

Table 16 ART Drug Resistance Prior to Index Date (Study Population)

Parameter	Statistic	ART naïve participants N=70 n(%)	ART experienced participants N=282 n(%)	Study population N=352 n(%)	P-value
Resistance gene examination					
	n	70	282	352	-

	Participants with at least one resistance gene examination	13(18.6)	29(10.3)	42(11.9)	0.056
Drug resistance					
	n	13	29	42	-
	Participants with at least one drug resistance	0	0	0	-
	Resistance to NNRTIs	0	0	0	-
	Resistance to NRTIs	0	0	0	-
	Resistance to PIs	0	0	0	-
	Resistance to INSTIs	0	0	0	-

Note: The denominator (n) of the resistance gene examination is the number of participants with available data in study population. The denominator (n) of the drug resistance, resistance to NNRTIs, resistance to NRTIs, resistance to PIs and resistance to INSTIs is the number of participants who have accepted the resistance gene examination and with available data.
P-value: Comparison between ART naïve and experienced participants of the study population.

Table 17 ART Drug Resistance During the Observation Period (Study Population)

Parameter	Statistic	ART naïve participants N=70 n(%)	ART experienced participants N=282 n(%)	Study population N=352 n(%)	P-value
Resistance gene examination					
	n	70	282	352	-
	Participants with at least one resistance gene examination	12(17.1)	6(2.1)	18(5.1)	<0.001
Drug resistance					
	n	12	6	18	-
	Participants with at least one drug resistance	2(16.7)	2(33.3)	4(22.2)	0.569
	Resistance to NNRTIs	2(16.7)	0	2(11.1)	0.529
	Resistance to NRTIs	0	1(16.7)	1(5.6)	0.333

Resistance to PIs	0	1(16.7)	1(5.6)	0.333
Resistance to INSTIs	0	0	0	-

The denominator (n) of the resistance gene examination is the number of participants with available data in study population. The denominator (n) of the drug resistance, resistance to NNRTIs, resistance to NRTIs, resistance to PIs and resistance to INSTIs is the number of participants who have accepted the resistance gene examination and with available data.
P-value: Comparison between ART naïve and experienced participants of the study population.

As shown in Table 18, most participants (98.9%) were administrated with DELSTRIGO™ as DOR based regimen, and only 4 participants (1.1%) were treated with PIFELTRO™ and DELSTRIGO™ in different time periods in the study population. No participants only used PIFELTRO™ for 48±8 weeks. No significant difference of DOR based regimen pattern between the effectiveness analysis population and study population (p=0.969 when comparing DELSTRIGO™ administration). During the chart review process, no other ART was found to use in combination with DELSTRIGO™, such as dolutegravir (DTG), raltegravir (RAL). No document showed that other cART regimens were used if the participant stopped DOR based regimen within 60 days.

A total of 9 (2.6%) participants discontinued of PIFELTRO™ or DELSTRIGO™ treatment during the observation period (A ≥60-day gap for PIFELTRO™ or DELSTRIGO™ was considered as discontinuation of treatment per protocol). Only 4 participants were documented the reasons for discontinuation, which included 1 participant with poor drug tolerance, 1 participant with financial situation, and other two participants with others (i.e., participants willingness, et al) (Table 19).

As shown in Table 20, the proportions of participants with adherence ≥80% were 90.1% and 91.5% during the period of 48±8 weeks in the study population and the effectiveness analysis population, respectively. The effectiveness for participants with adherence ≥80% was described in "Section 10.4.1Proportion of participants with VS at week 48±8 following PIFELTRO™ or DELSTRIGO™ administration".

Table 18 PIFELTRO™ or DELSTRIGO™ Prescription and Other ART Prescription During the Observation Period

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	Study population N=352 n(%)	P-value
PIFELTRO™ or DELSTRIGO™ prescription				
	n	271	352	-

Parameter	Statistic	Effectiveness analysis population N=271 n(%)	Study population N=352 n(%)	P-value
	Participants with at least one PIFELTRO™ or DELSTRIGO™ prescription	271(100.0)	352(100.0)	-
	Doravirine tablets (PIFELTRO™)	0	0	-
	Doravirine, Lamivudine and Tenofovir Disoproxil Fumarate Tablets (DELSTRIGO™)	268(98.9)	348(98.9)	0.969
	PIFELTRO™ and DELSTRIGO™ combined	0	0	-
	PIFELTRO™ and DELSTRIGO™ in different time periods	3(1.1)	4(1.1)	0.969
Other drug prescription if the participant was prescribed with other ART except PIFELTRO™ or DELSTRIGO™*				
	n	271	352	-
	Participants with at least one other drug prescription	0	0	-
	NNRTIs	0	0	-
	NRTIs	0	0	-
	PIs	0	0	-
	INSTIs	0	0	-
	FIs	0	0	-

Note: The denominator (N) is the number of effectiveness analysis population or study population, respectively.
*It refers to any other ART except PIFELTRO™ and DELSTRIGO™ within 60 days.
P-value: Comparison between the effectiveness analysis population and the study population.

Table 19 PIFELTRO™ or DELSTRIGO™ Discontinuation (Study Population)

Parameter	Statistic	Total N=352 n(%)
Discontinuation		
	n	352
	Participants with discontinuation	9(2.6)
Reason for discontinuation		
	No record	5(55.6)
	Poor drug tolerance of participants	1(11.1)
	Financial situation	1(11.1)
	Previous treatment failure	0
	Drug-drug interaction	0
	Simplified medication regimen	0
	Pregnancy	0
	Others	2(22.2)

Note: The denominator (N) for discontinuation is the number of study population.
The denominator for reason for discontinuation is the number of participants with discontinuation.

Table 20 Adherence for DOR in the Regimen

Adherence	Effectiveness analysis population N=271 n (%)	Study population N=352 n (%)
n	271	352
Adherence ≥80%	248(91.5)	317(90.1)
Adherence <80%	23(8.5)	35(9.9)

Note: The denominator (n) is the number of participants with available data in effectiveness analysis population or study population, respectively

10.5 Other analyses

Not applicable in this report.

10.6 Adverse events/adverse reactions

This is a retrospective observational study using medical chart review with the objective of assessing the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. Although adverse events (AEs) and product quality complaints (PQCs) were not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs must be reported. For example, during review of medical records or physician

notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE or PQC to PIFELTRO™, DELSTRIGO™ or any other sponsor product is identified, the AE/PQC must be reported. For the purpose of this study, as defined in the study protocol, the term AE includes serious adverse reactions (SARs), non-serious adverse reactions (NSARs), health outcome indicators (HOIs) that meet criteria for SAR/NSAR and special situations. Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as SARs/NSARs. During review of secondary data, causality should never be assigned retrospectively (details were provided in Section 9 Management and Reporting of Adverse Events/Adverse Reactions in the Protocol).

During the study period, 26 AEs from 18 participants (5.1%) were reported to the sponsor, which were extracted from EMR and other data sources according to the protocol. Hepatic function abnormal or hepatic failure (8/26) were reported as the most frequent AEs, followed by insomnia (3/26), dizziness (2/26), diarrhoea (2/26), hyperuricaemia (2/26), neutrophil count decreased (2/26), and others reported once (blood glucose increased, nausea, creatinine renal clearance decreased, protein urine present, abnormal dreams, haematuria, hyperlipidaemia). There were no PQCs (with or without AE), special situations (regardless of causality), or spontaneously reported AEs/PQCs for sponsor products observed in this study (Listing 5 in Annex 3).

All of the AEs reported among participants were non serious events, only 2 were moderate, the rest 24 were mild. Among these 26 AEs, 17 events were recovering/recovered and 9 events were not recovered. The most commonly reported AEs were hepatic function abnormal (n=6) and hepatic insufficiency (PT: hepatic failure, n=2). No relevant clinical symptoms were reported for all these cases. Similar abnormalities of hepatic (e.g., increased ALT, AST, ALP, total bilirubin, etc.) indicators were also reported in two previous phase III trials regarding PIFELTROTM/DELSTRIGOTM (DRIVE-FORWARD & DRIVE-AHEAD) according to the local label. Other frequently reported AEs such as insomnia, dizziness, and diarrhea, were also already reported in previous pivotal studies and described in local label. No potential safety signal was identified in this study.

11 DISCUSSION

11.1 Key results

This multi-center, retrospective study evaluated the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. It was found to be an effective treatment for Chinese adult living with HIV-1, regardless of whether they were treatment-naïve or experienced, in real-world settings. In a general population of PLWH initiating PIFELTRO™ or DELSTRIGO™, doravirine-containing HAART achieved an VS rate of 93.7% (95% CI: 90.8%, 96.6%) after 48±8 weeks' treatment. Similar results have been reported for ART-naïve and experienced participants at week 48±8: 90.0% (95% CI: 82.4%, 97.6%) of ART naïve participants; 94.8% (95% CI: 91.8%, 97.8%) of ART experienced participants regardless of VS at baseline. No significant difference in the proportion of VS between the ART naïve and the ART experienced participants. Subgroup analysis classified by virologic suppression before DOR initiation also reported similar results: 90.9% (95% CI: 84.0%,

97.8%) of participants who were ART naïve participants or ART experienced participants without VS before DOR initiation; 93.9% (95% CI: 88.2%, 99.7%) of experienced participants who could be confirmed VS before DOR initiation. No significant difference in the proportion of VS between the two sub-groups. When only including participants with adherence ≥80% during the period of 48±8 weeks, 94.0% (95% CI: 91.0%, 96.9%) of participants achieved VS. No participants experienced protocol-defined virologic failure. DELSTRIGO™ and PIFELTRO™ were well tolerated, 5.1% (18/352) of the participants had nonserious AEs. No SAE or severe AEs were reported during the study period.

The study also conducted sensitivity analysis to assess the impact of different measurements of VL (HIV-1 RNA) on primary endpoint. In the sensitivity analysis which used the last available virologic result for a participant with multiple virologic results at week 48±8, 94.1% (95% CI: 91.3%, 96.9%) of participants achieved VS. In the sensitivity analysis which included persons for whom an assay with LLOD of 100 copies/mL was used and who had VL <100 copies/mL at baseline, but would exclude someone for whom an assay with LLOD of 50 copies/mL was used and who had a VL between 51 and 99 copies/mL, 94.3% (95% CI: 88.8%, 99.7%) of ART experienced participants who could be confirmed VS before DOR initiation achieved VS at week 48±8. In the sensitivity analysis which used the adherence cutoff of at least 95%, 94.0% (95% CI: 90.9%, 97.2%) of participants achieved VS. The proportion of participants with adherence ≥95% achieving VS was similar to those with adherence ≥80% at week 48±8.

Only 18 (5.1%) participants had at least one genotypic drug resistance testing during observation period among study population. Of the 18 participants, a total of 4 participants were found to have genotype-specific drug resistance during observation period, including 2 (16.7%) ART naïve and 2 (33.3%) ART experienced participants, which included 2 participants with resistance to NNRTIs but no resistance to DOR, 1 participant with resistance to PIs, and 1 participant with resistance to NRTIs. The two participants with resistance to NNRTIs did not achieve VS at week 48±8. The participants with resistance to PIs achieved VS at week 48±8 and the participants with resistance to NRTIs didn't have available virologic result at week 48±8. Notably, among the other 14 participants without drug resistance, 10 participants received drug resistance testing at baseline and 8 out of 10 participants achieved VS at week 48±8, 1 out of 10 participants didn't have available virologic data at week 48±8, and 1 out of 10 participants had two VL testing results at week 48±8 (one was 64.3 copies/mL, another one was TND), which might be considered as a blips; 4 participants received drug resistance testing after 24 weeks and 2 out of 4 participants didn't have available virologic data at week 48±8, 1 out of 4 participants couldn't be regarded as VS or not for whom an assay with the LLOD of 250 copies/mL at week 48±8, and 1 out of 4 participants achieved VS (<20 copies/mL) at week 48±8. This indicates that participants who had evidence of no drug resistance no matter at baseline or during the treatment process were likely to achieve satisfactory therapeutic effects after 48 weeks of treatment.

The most common regimen within 1 year before the index date in the study population was dual NRTI+NNRTI (78.0%), followed by dual NRTI/1 NRTI+INSTI regimen (12.8%), dual NRTI+PI regimen (7.8%) and others (1.4%). A total of 59 participants (20.9%) had at least one change in cART regimen during the 1-year prior to index date. The cART regimen used

in the effectiveness analysis population before the index date was similar to that of the study population.

Most participants (98.9%) were administrated with DELSTRIGO™ as DOR based regimen, and only 4 participants (1.1%) were treated with PIFELTRO™ and DELSTRIGO™ in different time periods in the study population. No participants only used PIFELTRO™ for 48±8 weeks. No significant difference of DOR based regimen pattern between the effectiveness analysis population and study population. A total of 9 (2.6%) participants discontinued of PIFELTRO™ or DELSTRIGO™ treatment during the observation period (A ≥60-day gap for PIFELTRO™ or DELSTRIGO™ was considered as discontinuation of treatment per protocol).

11.2 Limitations

The study has several limitations. As this is not a comparative effectiveness study, it is not designed to compare specifically PIFELTRO™ or DELSTRIGO™ treatment with other cART regimens. With this retrospective study design, the VS may be over- or underestimated, due to factors such as adherence, persistence and possible unknown resistance to NNRTIs and other drugs included in ART, as well as unavailability of VL to be included, given that some participants make a return visit irregularly and may miss VL testing in the target time window (week 48±8).

Unlike the study medication diary in clinical trials, adherence through the prescription monitoring in our study would result in inaccurate measurement of adherence. For example, participants may forget refill, drop the medicine or forget to take after refill, which were regarded as adherence through the prescription monitoring. The inherent limitation of retrospective study design may restrict investigators from reminding participants to take their medicines timely. Thus in our study the effectiveness endpoint calculation didn't take prescription monitoring data into consideration but only use for the sensitivity analysis, which means all the participants who had available virologic information at week 48±8 were assumed to have substantial adherence to be evaluated for effectiveness. However, we found in clinical practice most clinicians would conduct routine participants management to remind participants to take the medicines regularly (wide variation in how frequently), which helped to mitigate the bias to some extent.

In addition, the restrictive exclusion criteria also limited information on the genotype-specific drug resistance in the study population. In the study only participants with evidence of resistance to NNRTIs and other drugs included in ART before index date would be excluded, however, genotypic resistance testing was only performed in only 42 of the 352 study participants. Though we searched any evidence related to resistance to NNRTIs and other drugs included in ART based on multiple data sources to avoid including participants with resistance to NNRTIs, it is still likely to include participants with potential resistance to NNRTIs and other drugs included in ART, preventing conclusions being drawn on the reason for the unsuccessful VS of this treatment.

The included hospitals were not randomly selected and may not be a representative sample of the total participants administered with PIFELTRO™ or DELSTRIGO™. The hospital

selection was based on the operation difficulty, potential number of HIV participants and potential use of PIFELTRO™ or DELSTRIGO™. This study aims to select hospital with more potential HIV participants and use of PIFELTRO™ or DELSTRIGO™ to meet the target sample size. There were eventually seven sites among which 78.7% of participants were from western regions in China, which may not represent the distribution of participants using PIFELTRO™ or DELSTRIGO™ in China. One of the main strengths of this multicenter study is the large sample size of participants in a real-life clinical setting rather than a clinical trial in China. Moreover, data were from clinic records of 1024 participants receiving PIFELTRO™ or DELSTRIGO™ at seven hospitals, and the investigators contacted all eligible participants who had been treated for at least 24 weeks unselectively until enrollment completion, and all the participants who signed informed consent or were authorized informed consent exemption by IRB/ERC had been included in our study. But some participants make a return visit irregularly and may miss VL testing in the target time window (week 48±8), thus the participants with unavailable VL at week 48±8 or can't be confirmed as virologic failure before week 40 by investigators weren't evaluated in the effectiveness analysis. In summary, though the study has some limitations, it is unlikely to have a big impact on the effectiveness evaluation and the generalizability of the study results.

11.3 Interpretation

Clinical trials remain the most effective method for evaluating the safety and efficacy in drug development and approval. However, the enforcement of strict inclusion and exclusion criteria may lead to selection bias and a highly selective study population. In contrast, real-world studies refer to data collected from daily life of broader populations treated in different clinical settings outside the scope of tightly controlled Randomized Controlled Trials (RCTs). Thus, it remains important to conduct post-marketing surveillance and collect data from the real world. This is especially the case for participant groups not represented in the respective RCTs. In the present study, with the inclusion and exclusion criteria consistent to the approved labels, the doravirine-containing HAART proved to be an effective treatment in persons living with HIV-1 regardless of VL at baseline in China. Among the participants who were administered PIFELTRO™ or DELSTRIGO™, it achieved the VS rate of 93.7% after 48±8 weeks' treatment. Similar results have been observed in ART-naïve and experienced participants (90.0% for ART naïve participants and 94.8% for ART experienced participants regardless of VS before DOR initiation). Above results show that they are similar to or higher than the point estimates than the results in pivotal clinical trials no matter in treatment-naïve participants (84% of PIFELTRO™ in DRIVE-FORWARD, 84.3% of DELSTRIGO™ in DRIVE-AHEAD) or in treatment-experienced participants (90.8% of DELSTRIGO™ for participants with VL <50 copies/mL at baseline in DRIVE-SHIFT). The difference results from clinical trials may be at least partly explained by adherence measures and administration, available baseline genotypic drug resistance testing data, and definition of treatment failure, etc., all of which were the inherent limitations of real-world studies. Thus, making a direct comparison to the results of clinical trials is not possible.

Doravirine-containing HAART also showed consistent results in PLWH in other real-world studies. In UK, using similar retrospective chart review study design, 90% (9/10) of ART naïve participants and 95% (244/256) of ART experienced participants treated with DOR-containing ART had an undetectable VL (<50 copies/mL) at 6 months [Ref. 5.4: 08RF7W].In

France, in 50 highly ART-experienced PLWH with long-term VS, doravirine/lamivudine regimens can maintain high levels of VS (98.0%) at week 48, and CD4+ T cell count was also restored [Ref. 5.4: 08RF7P]. Another study from Italy retrospectively investigated 132 participants who switched to DOR-containing/-based regimens, the proportion of undetectable HIV-1 RNA was 94.3% (49/52) at week 24, and confirmed a favorable impact from DOR on lipid profile and a neutral impact on weight gain [Ref. 5.4: 08RF7Z]. A national prospective cohort from Netherlands (ATHENA National Observational Cohort Study) assessed the effectiveness of switching to DOR based ART in well suppressed participants without previous virologic failure, showing non-inferior compared with continuing non-doravirine-containing regimens after 2 years in a real-world setting [Ref. 5.4: 08RF83]. In Spain, at week 48 the effectiveness of DOR plus two NRTI was between 73.3% and 90.8% for experienced participants with 91% of VS at baseline by intention-to-treat analysis, where non-complete or missing data were considered treatment failure [Ref. 5.4: 08RF7S]. In another real-world study of NNRTI class conducted in China, e.g., ANV plus two NRTIs showed 83.6% of VS at week 48 among 122 ART naïve participants [Ref. 5.4: 08RF7D].

PIFELTRO™ and DELSTRIGO™ have been recommended as first-line ART regimens by China treatment guideline (2021 edition) [Ref. 5.4: 084HM7]. In the early 2023, DELSTRIGO™ was included in the NRDL, which would result in lower costs and increased willingness to use. It showed in our study 98.9% of participants only use DELSTRIGO™ and 1.1% of participants use PIFELTRO™ and DELSTRIGO™ in different time periods due to this reimbursement policy change. In this perspective, our study provided real-world data for PIFELTRO™ as a single entity and a FDC with 3TC and TDF (DOR/3TC/TDF). However, other studies provided more effectiveness data for DOR plus two NRTIs. In Spain, the effectiveness of DOR plus abacavir (ABC)/3TC or TDF/ FTC was 90.8% and 73.3%, respectively [Ref. 5.4: 08RF7S].

This study aims to select hospital with more potential HIV participants and use of PIFELTRO™ or DELSTRIGO™ to meet the target sample size, which are not well representative of people with HIV in China. Although all the data were from medical records at seven hospitals and the investigators contacted all eligible participants who had been treated for at least 24 weeks unselectively until enrollment completion to minimize the selection bias, unfortunately, unlike our expectation of exemption from obtaining written informed consent for all the participants due to medical chart review design, we were required to contact the participants before access to the detailed medical records, and only the exemption could be permitted after providing sufficient evidence for no response from participants. Under the circumstance, participants who refused the study, only had a verbal promise to come back to sign the informed consent, or had insufficient evidence for no response can’t be screened and involved in the study. In our study, the investigators contacted all eligible participants in the seven sites unselectively until enrollment completion. Eventually only the participants who signed informed consent or met the criteria for informed consent exemption approved by IRB/ERC had been included in our study.

11.4 Generalisability

This is the first post-marketing observational study conducted in China to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. The design is a retrospective chart review study conducted in seven hospitals which were not randomly selected, so the study population may not be a representative sample of the total participants administered with PIFELTRO™ or DELSTRIGO™ in China. However, this is the first real world study with the largest sample size for assessing effectiveness of doravirine-containing HAART in China. All the Chinese adult living with HIV-1 who initiated doravirine-containing HAART from August 2021 to September 2023 that met the inclusion and exclusion criteria were included in the study. The inclusion and exclusion criteria for this study are broader compared to clinical trials, which are consistent with the population specified in the package insert for PIFELTRO™ or DELSTRIGO™ in China.

This study aims to select hospital with more potential HIV participants and use of PIFELTRO™ or DELSTRIGO™ to meet the target sample size. There were eventually seven sites among which 78.7% of participants were from Yunnan, Guizhou and Sichuan, which makes the result from this study generalizable for western regions where participants were administered with PIFELTRO™ or DELSTRIGO™. However, in clinical practice all the clinicians would conduct routine management for participants with HIV and most participants have the chance to access information, education and services which benefit the adherence. Therefore, these regional differences of included participants are unlikely to impact the generalizability of the study results to other regions. In addition, the large sample size and strict supervision on study process contributed to a robust study.

12 OTHER INFORMATION

Not applicable in this report.

13 CONCLUSION

This is the first post-marketing observational study conducted in China to assess the effectiveness of doravirine included in HAART in Chinese persons living with HIV-1. Doravirine-containing HAART has shown an high overall effectiveness, that was estimated as 93.7% (95% CI: 90.8%, 96.6%) at week 48±8 in Chinese persons living with HIV-1, including ART naïve and ART experienced participants regardless of virologic suppression at baseline in this study, which is consistent with that reported in previous overseas studies in real-world settings.

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