BMC Infectious Diseases

STUDY PROTOCOL

Open Access

Clinical outcomes of dolutegravir treatment in people living with HIV in Brazil: protocol for the CODE cohort

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Abstract

The Clinical Outcomes of Dolutegravir Treatment in People Living with HIV in Brazil (CODE) cohort study is a multicenter, prospective, observational study designed to evaluate the safety and efficacy of Dolutegravir (DTG)-based antiretroviral therapy (ART) among people living with HIV across diverse settings in Brazil. With the recent global shift towards DTG as a preferred option for first-line ART, particularly in low- and middle-income countries, there is vital need for comprehensive real-world data to inform its widespread use. CODE aims to fill this knowledge gap by assessing the clinical outcomes of both ART-naïve and ART-experienced patients initiating DTG-based regimens, as well as those who have switched from non-DTG-based ART. The primary objective of this study is to determine the proportion of patients who discontinue DTG due to any adverse events, specifically focusing on metabolic and psychiatric outcomes. Secondary objectives include evaluating the rates of virological suppression, the occurrence of immune reconstitution inflammatory syndrome (IRIS), changes in body mass index (BMI), and the development of HIV drug resistance. The CODE cohort will enroll approximately 5000 participants from multiple clinical sites across Brazil, including 2500 ART-naïve individuals, 1000 patients switching to DTG-based regimens for various reasons, and a comparator group of 1500 individuals who initiated non-DTG-based ART between 2013 and 2016, before DTG was available in the country. Participants will be followed for up to 36 months, with data collection points at baseline, 6, 12, 24, and 36 months. This study is expected to generate critical insights into the long-term outcomes associated with DTG-based ART, particularly in real-world settings that reflect the complexities of routine clinical care. By providing robust data on the effectiveness and safety of DTG in a diverse patient population, the CODE study aims to contribute to the optimization of HIV treatment strategies both in Brazil and globally.

Key words: HIV-1, Dolutegravir, Outcomes, Brazil

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Introduction

The rapid expansion of access to antiretroviral therapy (ART) in low- and middle-income countries has been a significant milestone in the global fight against HIV. In Brazil, where ART has been universally available since 1996, the recent introduction of Dolutegravir (DTG)-based regimens as first-line therapy represents a critical advancement. The World Health Organization (WHO) guidelines now recommend DTG, combined with two nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir and lamivudine, as the preferred regimen for initiating ART [1–3]. However, despite the advantages of DTG, including its virologic potency, high barrier to resistance, and favorable tolerability profile, there remain critical gaps in understanding its long-term outcomes, particularly in real-world settings.

The CODE cohort study is designed to address these gaps by providing robust data on the clinical outcomes of DTG-based ART in a large cohort of people living with HIV in Brazil. This multicenter, prospective observational study will follow ART-naïve patients starting DTG-based regimens, those switching to DTG due to virological failure, and a comparator group of patients who initiated non-DTG-based ART before DTG was introduced in Brazil. The choice of treatments followed the recommendations of the Brazilian Guidelines for Antiretroviral Treatment of Adults [1].

Several specific concerns have emerged from recent studies that highlight the need for further investigation. For example, the rapid virologic suppression associated with integrase inhibitors (INIs) like DTG has been linked to an increased risk of immune reconstitution inflammatory syndrome (IRIS), particularly among patients with low CD4 cell counts at ART initiation, although other reports showed no difference in comparison with regimens based in other antiretroviral drugs. In European cohorts, INI-based regimens have been associated with a 2–3 fold increase in IRIS risk among patients with CD4 counts below 200 cells/mm^3. Moreover, observational studies have pointed to variable rates of DTG discontinuation due to central nervous system (CNS) and metabolic toxicities [4–10]. Given these potential risks, there is an urgent need to understand the broader implications of DTG use, especially as it becomes more widely available in settings with a high burden of late-stage HIV and co-infections like tuberculosis.

The Brazilian context offers a unique opportunity to study these issues. With a large and diverse population of people living with HIV, Brazil's healthcare system provides a natural laboratory for evaluating the real-life effectiveness and safety of DTG-based regimens. The CODE study aims to quantify the frequency of DTG discontinuation due to adverse events, evaluate virological suppression rates, assess clinical outcomes such as IRIS, weight gain, and CNS effects, and identify the development of drug resistance in patients on DTG-based therapy.

This study will follow a cohort of 5000 participants over 36 months, including 2500 ART-naïve individuals, 1000 ART patients switching to DTG for various reasons, and a retrospective cohort of 1500 individuals never took DTG. Despite the limitations inherent to the use of a historical control group, it is justified by the fact that this group is composed by participants that started treatment with the current first-line therapy (lamivudine + tenofovir + efavirenz, in a fixed-dose combination) before DTG was made available in Brazil. As the Brazilian guideline changed to introduce DTG-based regimens as the recommended therapy for initiation of ARV therapy, using a contemporary group on efavirenz-based regimen was not feasible [1]. The broad inclusion criteria and diverse participant population will allow for a comprehensive assessment of DTG's impact across various stages of HIV infection and treatment histories, and will provide more information on the emerging mutations of resistance to integrase inhibitors.

In summary, the CODE cohort study is poised to provide critical insights into the real-world outcomes of DTG-based ART in Brazil. By addressing the knowledge gaps related to DTG's safety and effectiveness, this study will contribute valuable evidence to guide treatment strategies in similar low- and middle-income country settings worldwide.

Materials and methods

Aim, design, and setting

The CODE cohort study is a multicenter, prospective observational study designed to assess the clinical outcomes of people living with HIV who are initiating or switching to Dolutegravir (DTG)-based antiretroviral therapy (ART) in Brazil. The study is conducted across multiple clinical sites, including major HIV treatment centers in the cities of Rio de Janeiro, Salvador, São Paulo, and Porto Alegre. Additional sites include clinics and hospitals in Caxias do Sul, Ribeirão Preto, Vitoria, Nova Iguaçu, Campinas, São Caetano do Sul, Natal and Botucatu (See Fig. 1). All sites are referral centers for HIV care.

Study population and sample size

The study aims to enroll a total of 5000 participants, distributed across four groups: Group 1 includes 2500 ART-naïve individuals starting a DTG-based regimen; Group 2 includes 500 patients on stable ART who switch to DTG-based regimens for any reason, and Group 3 includes 500 ART-experienced patients switching to DTG due to virological failure on their current regimen. The fourth Group [4] is a comparator group that includes

Fig. 1 Clinical sites for the CODE Study

data from 1500 patients who initiated non-DTG-based ART between 2013 and 2016 and have not switched to a DTG regimen. Participants will be followed for up to 36 months, with data collection points at baseline, 6, 12, 24, and 36 months. This large and diverse sample size is designed to ensure sufficient power to detect differences in clinical outcomes between the groups, particularly in terms of treatment discontinuation, virological suppression, and the incidence of adverse events.

Sample size calculations were based on a two-sample test of proportions to compare the cumulative discontinuation rates between these two groups. The significance level was set at a type I error rate (α) of 0.025 (one-sided), with a type II error rate (β) of 0.20, corresponding to a statistical power of 80% ($1 - \beta = 0.80$). Assuming a 12-month discontinuation rate of 10% in Group 1, the study is powered to detect a minimum absolute difference of 3.5% in discontinuation rates between the groups (i.e., 13.5% or higher in Group 4). The retrospective comparator group (Group 4) is critical to the CODE study's ability to assess the effectiveness and safety of DTG-based regimens by providing a benchmark of patients who initiated non-DTG-based ART between 2013 and 2016 under Brazil's prior treatment initiation guidelines.

Assuming a 10% discontinuation rate in Group 1 (DTG-initiating), a sample size of 1,500 in Group 4 provides 80% power to detect a minimum absolute difference of 3.5% (i.e., a 13.5% discontinuation rate in Group 4), using a one-sided test with $\alpha = 0.025$. This corresponds to an odds ratio of approximately 0.71, a clinically meaningful difference for assessing comparative safety and tolerability in real-world settings. This sample size ensures sufficient precision to detect small but important differences, particularly as we expect higher discontinuation rates in the historical non-DTG group. A sample of 1,500 participants ensures enough variation across patient characteristics and treatment settings to support generalizability and statistical power for multilevel modeling (e.g., accounting for site-specific effects). Furthermore, this number was chosen based on feasibility—retrospective data availability, completeness, and quality across multiple clinical sites participating in CODE. Selecting

1,500 participants balances the need for statistical power with the practicality of extracting high-quality longitudinal data from diverse historical records.

This sample size also allows for more robust propensity score matching or covariate adjustment in multivariable models to reduce confounding when comparing prospective DTG-treated participants to the historical control group.

Inclusion and exclusion criteria

Inclusion Criteria include: (1) documented HIV infection by plasma HIV RNA viral load, rapid HIV test, or any licensed ELISA test. If diagnosis was made by rapid or serological test a confirmation by an alternative method such as Western Blot, HIV culture, or HIV pro-viral DNA is required; (2) age ≥ 15 years; and (3) initiation of a DTG-based regimen or for the comparator Group 4, a non-DTG-based ART regimen between 2013 and 2016. In the three prospective groups, women of child-bearing potential must be willing to use effective contraceptive methods. Patients are excluded from the drug-naive Group 1 if they have previously used ART. Persons incarcerated or on compulsory detention for psychiatric or physical illness are excluded.

Patients with previous virological failures were eligible to enter the switch arm, if they met the inclusion criteria. Historical genotypes were retrieved from an existing, national databank on genotypic tests (RENAGENO) that stores the results of all resistance testing performed in the public health services in Brazil.

Participant selection and recruitment

Participants are being recruited from the clinical sites based on their eligibility and willingness to participate in the study. The selection process will ensure a heterogeneous population reflective of the broader HIV-positive population in Brazil. The broad inclusion criteria are designed to capture a wide range of patient characteristics, allowing for subgroup analyses and the identification of factors associated with specific outcomes.

Study procedures

At baseline, all prospective participants will undergo comprehensive assessments, including: collection of demographic data (e.g., age, gender, education level); documentation of HIV infection status, including CD4 + and CD8 + cell counts, and HIV RNA levels. A detailed medical history, including prior ART use, co-infections, and other relevant health conditions and a physical examination that includes weight, height, abdominal circumference, and blood pressure is taken. Laboratory evaluations include complete blood count (CBC), liver and renal function tests, fasting glucose and lipid profile, and urinalysis for proteinuria and blood samples are collected for plasma storage to facilitate future resistance testing. Finally, a Quality-of-Life assessment using the WHO QoL BREF is conducted for those switching to DTG-based regimens. Participants will be followed at 6, 12, 24, and 36 months (Table 1). During these visits, the following will be monitored: continued documentation of ART regimen and any changes, including reasons for switching or discontinuation; clinical evaluations, including measurement of vital signs, weight, and assessment of any new symptoms or adverse events; repeat laboratory tests to monitor HIV RNA levels, CD4 + and CD8 + counts, markers of liver and renal function, and assessments of adherence to ART (using the ACTG questionnaire for adherence assessment), and any concomitant medications. For those switching to DTG-based regimens, quality of life assessments are conducted at 6 and 12 months.

Participants in Group 4 are identified from existing clinical databases and patient records across the participating sites. Eligible participants must have initiated non-DTG-based ART within the specified timeframe (2013–2016) and must have adequate medical records that allow for the extraction of relevant clinical data. Inclusion criteria focus on ensuring that participants have consistent follow-up data available over the study period, with particular attention to ART regimen details, clinical outcomes, and laboratory results. Baseline data is extracted for each participant from the time of ART initiation, and includes: demographic information, baseline CD4 count, HIV RNA levels, and any comorbid conditions present at the time of ART initiation (Table 2). Baseline data also include details of the initial ART regimen, reasons for selecting the non-DTG-based regimen, and any contraindications to DTG that may have influenced treatment decisions. Follow-up data collection for this group corresponds to the same intervals used for the prospective groups: at 6, 12, 24, and 36 months after ART initiation, and includes: virological, immunological, clinical outcomes, adverse events and treatment modifications (Table 2).

Adverse events (AEs) and serious adverse events (SAEs) are recorded and reported according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1). All SAEs will be reported to the study sponsor (ViiV Healthcare) and Institutional Review Boards (IRBs) within 24 h of awareness.

Data management

Data will be collected and managed using the Research Electronic Data Capture (REDCap) system hosted at the University of New Mexico (UNM). REDCap is a secure, web-based application designed to support data capture for research studies, providing an interface for validated data entry, audit trails, and automated export procedures. The system includes encryption, password protection,

Table 1 Schedule of assessments for prospective groups 1, 2, and 3

Requirement	*Baseline	Follow-up visits			
		6 months	12 months	24 months	36 months
Informed consent	X				
Demographics, including education	X				
Documentation of HIV infection	X				
CD4 + cell count and CD4%/CD8 + cell count and CD8%	X	X***	X***	X***	X***
Targeted health history and clinical evaluation	X	X	X	X	X
Record of the highest CD4 + cell count (absolute and %) and HIV RNA documented in the medical record at any time in the past.	X				
Findings from genotyping or other form of acceptable ART resistance testing, if available	X	X	X	X	X
Recording of selected concomitant medications (see item 3.5.1)	X	X	X	X	X
Pregnancy status	X	X	X	X	X
Quality of life assessment (switch group)	X	X	X		
Use of alcohol and recreational drugs	X	X	X	X	X
Anthropometric measures**	X	X	X	X	X
Plasma Sample Storage	X				
HIV RNA level	X	X	X	X	X
CBC: hemoglobin, hematocrit, white blood cell count (WBC) with differential and platelets	X	X	X	X	X
Renal function measurement: serum creatinine	X	X	X	X	X
Liver function measurements: ALT, AST, alkaline phosphatase, total bilirubin and albumin	X		X	X	X
Glucose	X	X	X	X	X
Total cholesterol, LDL, HDL, triglycerides	X	X	X	X	X
Dipstick urinalysis for protein	X	X	X	X	X
DEXA and/or the assessment of body fat impedance (whenever possible)	X	X	X	X	X

*(< 60 days before participant´s study)

** Anthropometric measurements (weight, abdominal waist, hips and height (height only on visit 1)

*** If possible

60 days before or after the scheduled date

and internal quality controls to ensure the accuracy and completeness of data. Each clinical site will be responsible for entering data into REDCap, with regular monitoring and quality checks conducted by the study's Statistics and Data Coordinating Center (SDCC) at UNM.

Statistical analysis

Primary Analysis: The primary outcome is the proportion of treatment-naïve participants (Group 1) who discontinue DTG-based ART due to any event within 12 months, compared to those who initiated non-DTG-based ART (Group 4). This will be analyzed using a modified multivariable Poisson model, adjusting for potential confounders such as age, gender, race, and baseline CD4 count.

Secondary Analysis: Secondary outcomes include virological suppression rates, changes in body mass index (BMI), incidence of IRIS, and the development of drug resistance. These will be assessed using similar multivariable model, as well as linear mixed models for continuous outcomes such as BMI changes.

Exploratory Analysis: Exploratory outcomes, such as the frequency of cardiovascular events, new-onset diabetes, and quality of life changes, will be analyzed descriptively and use appropriate statistical tests for between-group comparisons.

Handling of Missing Data: Given the observational nature of the study, missing data is expected. The analysis will include strategies such as multiple imputation for missing data assumed to be missing at random (MAR) or completely at random (MCAR). Sensitivity analyses will be conducted to assess the impact of missing data on the study's findings.

The data will be assessed for whether data is missing at random (MAR), missing completely at random (MCAR), or missing not at random (MNAR). Mixed regression models will be used for analysis over time which uses all available data, given the MAR or MCAR assumptions are met. As a sensitivity analysis, multiple imputation methods may be applied to longitudinal data assumed to be MAR or MCAR to create complete data sets for mixed modeling. The results will be compared and those with better fit statistics will be reported. Multiple imputation would be performed using the chained equations approach available in IVEWare4. Alternatively, the propensity score method for monotone missing outcome data may be used should the data meet the assumptions for application.

Table 2 Schedule of assessments for restropective arm (Group 4)

Requirement	*Baseline	Follow-up visits			
		6 months	12 months	24 months	36 months
Informed consent	X				
Demographics	X				
Documentation of HIV infection	X				
CD4 + cell count and CD4%/CD8 + cell count and CD8%	X	X***	X***	X***	X***
Targeted health history and clinical evaluation	X	X	X	X	X
Record of the highest CD4 + cell count (absolute and %) and HIV RNA documented in the medical record at any time in the past.	X				
Findings from genotyping or other form of acceptable ART resistance testing, if available	X	X	X	X	X
Recording of selected concomitant medications (see item 3.5.1)	X	X	X	X	X
Pregnancy status	X	X	X	X	X
Use of alcohol and recreational drugs	X	X	X	X	X
Anthropometric measures**	X	X	X	X	X
HIV RNA level	X	X	X	X	X
CBC: hemoglobin, hematocrit, white blood cell count (WBC) with differential and platelets	X	X	X	X	X
Renal function measurement: serum creatinine	X	X	X	X	X
Liver function measurements: ALT, AST, alkaline phosphatase, total bilirubin and albumin	X	X	X	X	X
Glucose	X	X	X	X	X
Total cholesterol, LDL, HDL, triglycerides	X	X	X	X	X
Dipstick urinalysis for protein	X	X	X	X	X

*(< 60 days before participant´s study)

** Anthropometric measurements (weight, abdominal waist, hips and height (height only on visit 1)

*** If possible

60 days before or after the scheduled date

Ethical considerations

The study is being conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and local regulatory requirements. Ethical approval has been obtained from the IRBs at each participating site, and all participants will provide written informed consent prior to enrollment. Confidentiality will be maintained using coded identifiers, and data will be stored in secure, access-controlled databases. The study also includes provisions for the protection of vulnerable populations, such as adolescents and women of child-bearing potential.

Status and timeline of the study

Figure 2 presents a Consort Diagram of enrolled and followed patients, missed and pending visits, and number of withdrawals. As of September 1st, 2024, the CODE study has a total of 4,288 patients enrolled. Baseline data has been collected for 2,077 patients in Group 1, 508 in Group 2, 188 in Group 3, and 1,515 in Group 4. Six month visits have been completed for 67.3% (1398/2077), 91.5% (465/508), and 63.3% (119/188) patients in Groups 1, 2, and 3 respectively. Group 4 has completed 6 month data for 85.3% of 1515 patients enrolled. Data is also shown for the 12, 24, and 36 month visits.

Discussion

The CODE cohort study provides a unique opportunity to investigate the real-world outcomes of DTG-based ART among people living with HIV in Brazil. As a large, multicenter prospective observational study, CODE is poised to generate valuable data on the efficacy and safety of DTG-based regimens, particularly in diverse populations that may be underrepresented in randomized controlled trials. We expect this study will yield critical insights into the long-term outcomes of DTG-based ART, including the rates of treatment discontinuation due to adverse events, virological suppression, and the development of drug resistance. The primary finding of interest—the proportion of ART-naïve patients who discontinue DTG-based regimens—will provide essential information on the tolerability of DTG in real-world settings. Secondary outcomes, such as the frequency of metabolic and psychiatric events, will help elucidate the broader safety profile of DTG. The inclusion of ART-experienced patients and a retrospective comparator cohort of individuals on non-DTG regimens enhances the study's relevance by enabling a comparison across different treatment histories and clinical contexts. This will allow us to identify specific subgroups who may be at higher risk for adverse outcomes or who might benefit the most from DTG-based therapy. An important question that can be solved by CODE results regards the

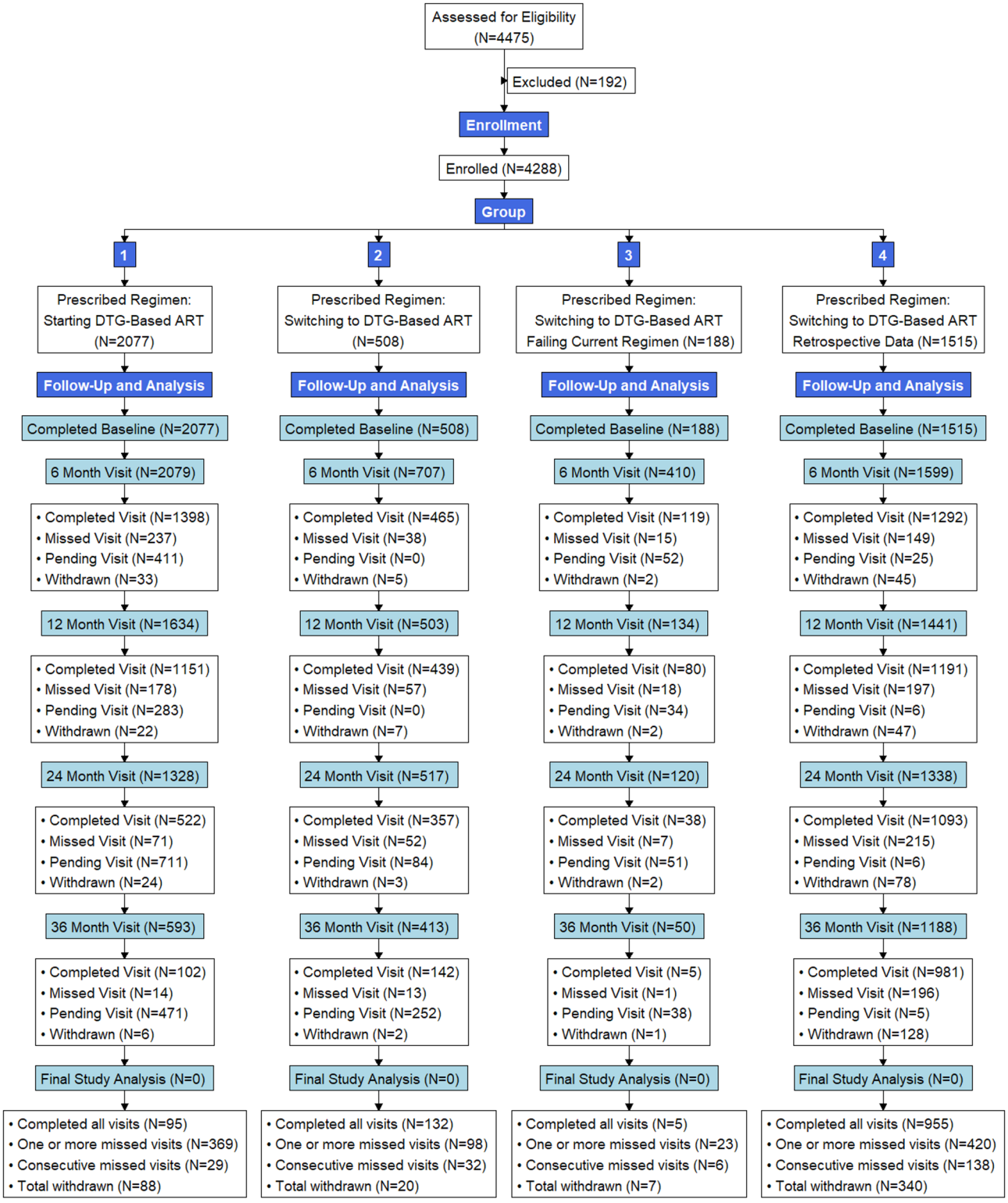

Fig. 2 Code Consort Diagram (as of 01 September 2024)

potential emergence of resistance to DTG in patients failing a DTG-based regimen, scarcely documented in countries with limited resources. In Brazil, the availability of free of costs genotypic tests across the country can help us to understand the magnitude and emergence of DTG resistance among this group of patients.

While the study's observational design offers the advantage of capturing real-world data, it also presents certain

limitations that must be acknowledged. First, the non-randomized nature of the study may introduce selection bias, as patients initiating DTG-based therapy may differ systematically from those on other regimens. We have attempted to mitigate this by using broad inclusion criteria and adjusting for potential confounders in our statistical analyses. However, residual confounding cannot be entirely ruled out. Another potential limitation is the reliance on clinical sites across different regions of Brazil, which may lead to variability in data collection practices and clinical management. To address this, we have implemented standardized protocols for data collection and adverse event monitoring, along with regular quality assurance checks conducted by the UNM SDCC. Missing data is an inherent challenge in any longitudinal study, particularly in a cohort as large and diverse as CODE. We have taken steps to minimize missing data through rigorous follow-up procedures and will use appropriate statistical techniques, such as multiple imputation, to handle any missing data that does occur. The historical control group, which is the study's comparator group may introduce bias, due to potential differences in patient populations and data quality. However, Brazilian guidelines for HIV treatment limit creation of a different control group using a different contemporary regimen. Finally, the observational nature of the study limits our ability to establish causal relationships between DTG use and the outcomes of interest. While we can identify associations, further studies, including randomized controlled trials, may be needed to confirm these findings and explore underlying mechanisms.

Future research directions

The findings from the CODE cohort study are expected to inform future research and clinical practice in several important ways. First, they will provide much-needed data on the safety and effectiveness of DTG in diverse populations, including those with late-stage HIV or co-infections such as tuberculosis and viral hepatitis. This is particularly relevant for low- and middle-income countries, where such data are often lacking.

Second, the study's focus on real-world outcomes, such as treatment discontinuation and the development of drug resistance, will contribute to a better understanding of the long-term implications of DTG use in routine clinical practice. This could lead to the refinement of treatment guidelines and the development of strategies to optimize the use of DTG in different patient populations.

In addition to the immediate findings, the CODE study will create a valuable biorepository of plasma samples that can be used for future research on HIV drug resistance and other virological and immunological outcomes. This resource will facilitate ongoing investigations into the mechanisms of DTG resistance and the identification of biomarkers for adverse outcomes.

Dissemination and impact

The results of the CODE cohort study will be disseminated through peer-reviewed publications, conference presentations, and reports to national and international health agencies. We aim to share our findings with a wide audience, including clinicians, researchers, policymakers, and community stakeholders, to maximize the study's impact on HIV treatment and care.

Given the global shift towards DTG-based regimens, particularly in resource-limited settings, the findings from CODE are expected to have significant implications for the management of HIV worldwide. By providing robust, real-world data on the safety and effectiveness of DTG, the study will contribute to the evidence base needed to guide treatment decisions and improve patient outcomes.

In conclusion, the CODE cohort study represents a critical step forward in our understanding of DTG-based ART in diverse and often underrepresented populations. While the study has certain limitations, its strengths lie in its large, multicenter design, comprehensive data collection, and focus on real-world outcomes. The knowledge gained from this study will be invaluable in shaping the future of HIV treatment in Brazil and beyond.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11700-0.

Supplementary material 1.

Acknowledgements

We acknowledge the following individuals who contributed expertise and assistance for the study: Benjamin Chase for early data management assistance, and Mariana Herring for expert translation and communication services.

Supporting information: Strobe checklist.

Authors' contributions

CB, EL and KP conceptualized the study and study design. CB, KP, CM-K, JE, MC, AA, and BC developed the data collection methods, and analytic approach. All Brazilian authors (CB, EL, CS, FB, MVGL, AR, SW, VM, TR, AN, RDS, MBB, TN, KM, MP, FL, ES) are involved in data collection. The manuscript was written by KP, CB and CM-K, and all other authors reviewed and provided input and editing to the writing.

Funding

The study was funded by a grant from ViiV Healthcare/GSK Brazil (GSK-212964) received by Fundação Bahiana de Infectologia.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval has been obtained from the IRBs at each participating site, and all participants will provide written informed consent prior to enrollment.

Consent for publication
Not aplicable.

Competing interests
CB: Research grants: CNPq, GSK, Pfizer, Janssen. All but CNPq grants were awarded to Fundação Bahiana de Infectologia; Speaker and Advisory board (Gilead, GSK, MSD); SCW: Advisory Boar (ViiV); VM: Speaker (GSK, Gilead, Janssen); ANB: Speaker (Abbvie, Amgen-Bergamo, Astrazeneca, Boehringer Ingelheim, Celltrion, Dr. Reedys, Eurofarma, Gilead, GSK-ViiV, Janssen, Knigth Therapeutics, Moderna, MSD, Pfizer, Procter Gamble, Roche, Sanofi Pasteur, S. C. Johnson Johnson, Takeda, e Wyeth); KP: Has received research grants from the U.S. National Institutes of Health, and U.S. Centers for Disease Control and Prevention. All grants were awarded to the University of New Mexico. RZ: GSK employee; BJ: ViiV Healthcare employee.

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Received: 28 January 2025 / Accepted: 15 September 2025
Published online: 08 October 2025

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