Effectiveness of bi-monthly long-acting injectable cabotegravir and rilpivirine as maintenance treatment for HIV-1 in the Netherlands: results from the Dutch ATHENA national observational cohort

*Vita W Jongen, Ferdinand W N M Wit, Anders Boyd, Arne van Eeden, Annemarie E Brouwer, Robert Soetekouw, Rachida El Moussaoui, Janneke Stalenhoef, Kim C E Sigaloff, Tatiana Mudrikova, Jet Gisolf, David Burger, Annemarie M J Wensing, Marc van der Valk, on behalf of the ATHENA National Observational HIV Cohort**

Lancet HIV 2025; 12: e40–50

See **Comment** page e5

*ATHENA National Observational HIV Cohort members listed in the appendix (pp 9–11)

Stichting HIV Monitoring, Amsterdam, Netherlands (V W Jongen PhD, F W N M Wit PhD, A Boyd PhD, Prof M van der Valk PhD); **Department of Infectious Diseases, Public Health Service Amsterdam, Netherlands** (V W Jongen, A Boyd); **Department of Infectious Diseases, Amsterdam Infection & Immunity Institute, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, Netherlands** (F W N M Wit, A Boyd, Prof M van der Valk, K C E Sigaloff PhD); **DC Klinieken, Amsterdam, Netherlands** (A van Eeden MD); **Elisabeth Twee Steden Ziekenhuis, Tilburg, Netherlands** (A E Brouwer PhD); **Spaarne Ziekenhuis, Haarlem, Netherlands** (R Soetekouw MD); **Maasstad Ziekenhuis, Rotterdam, Netherlands** (R El Moussaoui MD); **OLVG, Amsterdam, Netherlands** (J Stalenhoef PhD); **Translational Virology, Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands** (T Mudrikova MD, A M J Wensing PhD); **Rijnstate Ziekenhuis, Arnhem, Netherlands** (J Gisolf PhD); **Department of Pharmacy, Radboud UMC Institute of Medical Innovation, Radboud University Medical Center, Nijmegen, Netherlands** (Prof D Burger PhD); **Ezintsha, Department of Health, University of the Witwatersrand, Johannesburg, South Africa** (A M J Wensing);

Summary

Background Real-world data showing the long-term effectiveness of long-acting injectable cabotegravir and rilpivirine are scarce. We assessed the effectiveness of cabotegravir and rilpivirine in all individuals who switched to cabotegravir and rilpivirine in the Netherlands.

Methods We used data from the ATHENA cohort, an ongoing observational nationwide HIV cohort in the Netherlands. In the primary analysis, we matched individuals who commenced cabotegravir and rilpivirine and had no history of virological failure (ie, one or more measurements of a plasma HIV RNA ≥1000 copies per mL; hereafter referred to as exposed) 1:2 with individuals using oral antiretroviral therapy (ART; hereafter referred to as unexposed). We assessed the effectiveness of cabotegravir and rilpivirine using restricted mean survival time (RMST) until loss of virological control (one or more measurements of plasma HIV RNA ≥200 copies per mL). In the secondary analysis, we assessed loss of virological control in individuals who commenced cabotegravir and rilpivirine with previous virological failure or unsuppressed HIV-1 RNA at cabotegravir and rilpivirine initiation, or both.

Findings In primary analysis, 585 exposed and 1170 unexposed individuals were included between Feb 27, 2018, and Aug 17, 2023. Median follow-up was 1·3 years (IQR 0·9 to 1·7). 14 exposed (2%) and 29 unexposed (2%) individuals had a loss of virological control, with no difference in RMST (difference=0·026, 95% CI –0·029 to –0·080). Seven (50%) exposed individuals re-suppressed without a regimen change. Seven (50%) switched ART, and six (43%) of 14 had documented integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance. No unexposed individuals switched ART after loss of virological control. In the secondary analysis, 105 individuals were included between July 1, 2016, and Aug 17, 2023. During a median follow up of 1·4 years (IQR 0·8 to 1·8), nine (9%) had a loss of virological control, of which five (56%) had INSTI or NNRTI resistance.

Interpretation Switching to cabotegravir and rilpivirine was not associated with a higher risk of loss of virological control among individuals without previous virological failure compared with oral ART. The high risk of loss of virological control among individuals with previous virological failure or an unsuppressed HIV-1 RNA at cabotegravir and rilpivirine initiation warrants more careful monitoring.

Funding Dutch Ministry of Health, Welfare, and Sport.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

The introduction of combination antiretroviral therapy (ART) has significantly decreased the morbidity and mortality rates of HIV, and transformed HIV into a manageable chronic condition. Typically, ART is offered as a daily oral dual or triple drug combination, which requires high levels of adherence for durable virological suppression. However, adherence might be challenged by the fear of stigma or disclosure and the burden of daily pill-taking.[1–3] Decreased adherence can subsequently lead to a rebound in viraemia and increased risk of selection of resistance mutations and onward HIV transmission.[4,5]

Therapeutic options, including long-acting injectable ART, could be of interest to those confronted with these challenges.[6,7] Several clinical trials have shown the efficacy of injectable cabotegravir, an integrase strand transfer inhibitor (INSTI), in combination with rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), as maintenance treatment for HIV.[8–10] Both a monthly and a bi-monthly treatment regimen have been proven non-inferior to oral ART[8,9,11] up to 152 weeks after initiation.[12,13] Although uncommon, the presence of at least two of the following factors at the initiation of cabotegravir and rilpivirine treatment increases the risk of virological

Research in context

Evidence before this study

Large clinical trials have shown the long-term effectiveness of injectable cabotegravir in combination with rilpivirine as maintenance treatment for HIV in well suppressed individuals without a previous virological failure. Both a once a month and once every 2 months treatment regimens were non-inferior to oral antiretroviral therapy (ART). To date, there are few data on the real-world effectiveness of long-acting cabotegravir and rilpivirine, especially for individuals with a previous virological failure or adherence challenges. We searched PubMed on April 23, 2024, with no language or date restrictions, using the terms ["HIV"] AND ["cabotegravir"] AND ["rilpivirine"]. We found eight publications describing the real-world effectiveness of long-acting cabotegravir and rilpivirine in a single-group design, of which four described the effectiveness of this treatment among individuals with a previous virological failure or adherence problems. Most studies reported data from a single centre and had small sample sizes. The real-world effectiveness of cabotegravir and rilpivirine compared with an oral ART regimen is unclear.

Added value of this study

Using data from the ATHENA cohort, consisting of data from more than 98% of all individuals with HIV in care in the Netherlands, we compared the effectiveness of cabotegravir and rilpivirine in well suppressed people with HIV without a previous virological failure, with individuals continuing standard oral ART. To this end, we matched 585 eligible exposed individuals who switched to cabotegravir and rilpivirine to 1170 unexposed individuals continuing oral ART. Our results showed that after a median of 1·3 years of follow-up, the risk of loss of virological control on cabotegravir and rilpivirine was similar to that among individuals continuing standard ART. Among the 14 exposed individuals who had a loss of virological control on cabotegravir and rilpivirine (2%), six had a confirmed virological failure with major integrase strand transfer inhibitor or non-nucleoside reverse transcriptase inhibitor resistance-associated mutations (RAMs) at the time of failure. None of the 29 individuals with a loss of virological control in the unexposed group (2%) had RAMs at time of failure. Additionally, we assessed the effectiveness of cabotegravir and rilpivirine in a separate cohort consisting of individuals with previous virological failure or a detectable HIV-1 RNA at cabotegravir and rilpivirine initiation. Loss of virological control in this study population (n=105) was substantially higher (9%). This study is the first real-world nationwide study to compare cabotegravir and rilpivirine with a standard oral ART. Our study fills an important gap regarding the unclear real-world effectiveness of cabotegravir and rilpivirine.

Implications of all the available evidence

Switching to cabotegravir and rilpivirine in well suppressed people with HIV without a previous virological failure is a durable and effective treatment option in a real-world setting. Among individuals with previous treatment failure or a detectable HIV-1 viral load, the risk of loss of virological control is considerably higher.

Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands
(A M J Wensing)

Correspondence to:
Dr Vita W Jongen, Stichting HIV Monitoring, Amsterdam 1105AZ, Netherlands
v.w.jongen@amsterdamumc.nl

See **Online** for appendix

failure: pre-existing rilpivirine resistance-associated mutations (RAMs), A6 HIV subtype, or a BMI of 30 kg/m² or higher.[14] In the Netherlands, long-acting cabotegravir and rilpivirine have been available since June 2021 as a bi-monthly treatment regimen. Previously, cabotegravir and rilpivirine were available in clinical trial settings.

Although clinical trials have shown long-term efficacy,[12,13] real-world data on the effectiveness of long-acting cabotegravir and rilpivirine are few.[15–18] Thus far, clinical trials have included people with HIV without a history of treatment failure and only two small observational cohort studies have reported on the effectiveness of cabotegravir and rilpivirine in individuals with previous virological failure or adherence challenges.[18,19] This absence of data limits the generalisability to people with HIV who might benefit the most from long-acting ART—namely, those with decreased adherence or a history of multiple treatment failure.

We aimed to assess the loss of virological control and confirmed virological failure among people with HIV using long-acting cabotegravir and rilpivirine with no previous virological failure (ie, no previous plasma HIV RNA ≥1000 copies per mL followed by a regimen change or detected RAMs, or both) and compared this with a matched group of individuals using a standard ART regimen using data from a national cohort of people with HIV. Furthermore, we assessed the effectiveness of cabotegravir and rilpivirine specifically in individuals with previous virological failure or a detectable HIV-1 RNA, or both, at the initiation of cabotegravir and rilpivirine.

Methods

Study design

In the Netherlands, HIV care is provided by 24 designated treatment centres across the whole country. The HIV Monitoring Foundation (Stichting HIV Monitoring) is tasked by the Dutch Ministry of Healthcare, Welfare and Sports to monitor and report on all aspects of HIV care for people with HIV in the Netherlands. Data collection was initiated in 1998 and data are prospectively collected in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, which captures data from more than 98% of all people with HIV in care in the Netherlands.[20]

People entering HIV care received written material about participation in the ATHENA cohort, after which they were asked to consent verbally to the use of their routinely collected medical data for research and monitoring (opt-in procedure). Participants could withdraw their consent at any time. Data collection was

approved by the boards of all participating centres. Only routinely collected data were used for this analysis and therefore no additional review or consent were required.

Participants

For the present study, we included all individuals who initiated cabotegravir and rilpivirine from Feb 27, 2018, to Aug 17, 2023. Data collection for ATHENA is continuous, but we used clinical data collected from Feb 27, 2018, to Feb 14, 2024. An oral lead-in with once per day 30 mg cabotegravir and 25 mg rilpivirine for at least 28 days was optional. An initial intramuscular injection of 600 mg cabotegravir and 900 mg rilpivirine was administered, after which the second 600 mg cabotegravir and 900 mg rilpivirine injection was administered 1 month later and all subsequent injections administered once every 2 months. Injections could be administered within 7 days from the scheduled injection dates, according to the registration label.[21]

In the primary analysis, we conducted an exposure-matched study and included individuals on the basis of the following inclusion criteria: no episodes of virological failure before cabotegravir and rilpivirine initiation (ie, no previous plasma HIV RNA ≥1000 copies per mL followed by a regimen change and no detected INSTI or NNRTI RAMs), their first ART regimen was not cabotegravir and rilpivirine, their last measured HIV-1 RNA viral load before cabotegravir and rilpivirine initiation was less than 200 copies per mL, a standard dual or triple ART regimen was used before cabotegravir and rilpivirine initiation, and they were 18 years of age or older. These individuals are hereafter referred to as exposed. We matched all exposed individuals 1:2 to people with HIV on standard-of-care oral ART (hereafter referred to as unexposed). Unexposed individuals were eligible for matching when they had a routine clinical visit with a viral load measurement within 3 months of the date that the matched exposed individual switched to cabotegravir and rilpivirine and had no episodes of virological failure before the matching date. Matching was done on the following variables: ART class of the anchor drug, age, sex at birth, HIV acquisition category (through sexual contact with same or opposite sex), time since ART initiation (categorised into 6-month periods), lowest pre-ART CD4 cell count (categorised as <200 cells per μL, 200–499 cells per μL, or ≥500 cells per μL), and highest pre-ART viral load (categorised as <100 000 or ≥100 000 copies per mL). Exposed individuals using a dual regimen without an NRTI were matched to unexposed individuals also using a dual regimen. If pre-ART CD4 cell counts were missing, the CD4 cell count measured at study entry was used (using the same categories). If pre-ART viral load was missing, pre-ART viral load was not taken into account in the matching. We used exact matching for all variables, except for age (matched on closest age within 5 years). In the secondary analysis, we included individuals who commenced cabotegravir and rilpivirine off-label and had previous virological failure or unsuppressed HIV-1 RNA, or both, at cabotegravir and rilpivirine initiation.

Procedures

At enrolment into the ATHENA cohort, the following demographic information was collected: year of birth, country of birth, sex assigned at birth, gender identity (if different from sex at birth), and most likely transmission route of HIV (eg, sexual contact). Information about the date of HIV diagnosis was retrieved from the referral letter of the general practitioner or Centre for Sexual Health, from health records in the HIV treatment centre, or self-reported if no documentation was available.

Data on CD4 cell count, plasma HIV-1 RNA, and changes in ART were collected by trained clinical research associates in cooperation with HIV-treating physicians using an extensive, standardised protocol or imported directly from clinical records from all visits. HIV-1 sequence analysis was interpreted with the International Antiviral Society USA resistance tables[22] and the Comet subtype tool.[23] The resistance score was calculated using the Stanford algorithm. Information on the type of needle used for the intramuscular injections, genotypic resistance test results (if not present in the dataset), and cabotegravir and rilpivirine drug concentrations were extracted manually from the clinical records of all individuals who had a loss of virological control. In a steady state, the mean population trough concentration is 1·6 mg/L for cabotegravir and 0·066 mg/L for rilpivirine.[16] The first quartile is 1·12 mg/L for cabotegravir and 0·032 mg/L for rilpivirine. Cabotegravir and rilpivirine concentrations of less than their respective first quartile were classified as subtherapeutic.[16]

Statistical analysis

We defined baseline as the start date of cabotegravir and rilpivirine treatment for exposed individuals and the clinic visit date closest to the matched cabotegravir and rilpivirine start date for unexposed individuals. Follow-up constituted all visits with HIV-1 RNA measurements until loss of virological control, discontinuation of cabotegravir and rilpivirine (for exposed individuals), ART switch (for unexposed individuals), or last clinical visit, whichever occurred first. Individuals who had no clinical data after baseline were excluded. Sociodemographic and HIV-related characteristics at baseline were compared between exposed and unexposed individuals using multilevel logistic regression with a random effect for the paired exposed and unexposed individuals.

We assessed loss of virological control (defined as one or more measurements of plasma HIV RNA ≥200 copies per mL) among exposed and unexposed individuals. We calculated the cumulative probability of loss of virological control using Kaplan–Meier methods. Time-at-risk started at date of first exposure to cabotegravir and rilpivirine—namely, the start date of the oral lead-in or the start date of the injections if not using an oral lead-in. We used

a parametric proportional hazards model with a piecewise exponential survival function accounting for matched pairs using a random effect to model loss of virological control. We also estimated the restricted mean survival time (RMST; ie, survival time until loss of virological control) and the restricted mean time lost (ie, survival time lost up to the largest observed event time) using the strmst2 command in STATA.[24,25] We calculated the absolute difference between exposed and unexposed in RMST and restricted mean time lost. We additionally assessed confirmed virological failure, defined as two or more measurements of plasma HIV RNA of 200 copies per mL

	Exposed (n=585)	Unexposed (n=1170)	p value*	Secondary cohort (n=105)†
Age	44 (35–54)	46 (36–55)	0·033	43 (35–53)
Gender				
Men	531 (91%)	1064 (91%)	NA	75 (71%)
Women	53 (9%)	106 (9%)	..	30 (29%)
Transgender women	1 (<1%)	0	..	..
Men who have sex with men	448 (77%)	903 (77%)	NA	57 (54%)
Region of origin				
Netherlands	324/582 (56%)	719/1162 (62%)	0·087	54/104 (52%)
Europe, North America, and Australia	82/582 (14%)	137/1162 (12%)	..	9/104 (9%)
The Caribbean and Latin America	93/582 (16%)	145/1162 (12%)	..	17/104 (16%)
Sub-Saharan Africa	42/582 (7%)	86/1162 (7%)	..	17/104 (16%)
South Asia	16/582 (3%)	39/1162 (3%)	..	3/104 (3%)
Other	25/582 (4%)	36/1162 (3%)	..	4/104 (4%)
HIV subtype A6	4/260 (2%)	3/543 (<1%)	0·36	1/59 (2%)
BMI >30 kg/m^2	91/583 (16%)	124/1166 (11%)	0·0030	13 (12%)
Known rilpivirine-associated RAMs at baseline	0/255	2/536 (<1%)	NA	4/58 (7%)
Cumulative number of baseline factors associated with cabotegravir and rilpivirine failure‡				
0	491 (84%)	1041 (89%)	0·0029	88 (84%)
1	93 (16%)	129 (11%)	..	16 (15%)
>1	1 (<1%)	0	..	1 (1%)
ART class before or at the start of cabotegravir and rilpivirine therapy				
Dual therapy	88 (15%)	176 (15%)	NA	8 (8%)
INSTI-based triple	311 (53%)	622 (53%)	..	43 (41%)
NNRTI-based triple	158 (27%)	316 (27%)	..	22 (21%)
PI-based triple	28 (5%)	56 (5%)	..	15 (14%)
Non-standard§	0	0	..	17 (16%)
Years since HIV diagnosis	9·9 (6·3–14·9)	10·2 (6·4–15·8)	0·23	13 (7–21)
Years since the start of ART	8·6 (5·8–13·2)	8·7 (5·8–13·3)	NA	11 (5–20)
Nadir CD4 cell count, cells per µL	320 (200–510)	330 (204–510)	NA	240 (140–400)
CD4 at baseline, cells per µL	736 (570–926)	772 (590–987)	0·013	670 (482–955)
Previous AIDS diagnosis	77 (13%)	149 (13%)	0·80	24 (23%)
Blips before the start of follow-up¶	0/585	0/1167	0·83	0 (0–1)
Previous cumulative number of virological failure	NA	NA	NA	6 (2–15)

Data are n (%) or median (IQR). Data missing for exposed and unexposed individuals: region of origin (n=11), BMI (n=6), years since HIV diagnosis (n=5), years since the start of ART (n=5), nadir CD4 cell count before initiation (n=74), CD4 cell count at the start of follow-up (n=54), and blips before the start of follow-up (n=3). Data missing for secondary cohort: region of birth (n=1), BMI (n=21), nadir CD4 cell count before initiation (n=14), CD4 cell count (n=5), previous AIDS diagnosis (n=12), and viral load before the start of follow-up (n=3). ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. RAM=resistance-associated mutation. *p values were estimated using multilevel logistic regression with a random effect for the paired exposed and unexposed individuals. †The secondary cohort comprised the individuals included in the secondary analysis—namely, individuals who commenced cabotegravir and rilpivirine and had previous virological failure or unsuppressed HIV-1 RNA, or both, at cabotegravir and rilpivirine initiation. The resistance score was calculated using the Stanford algorithm. ‡Factors associated with cabotegravir and rilpivirine failure included a BMI of more than 30 kg/m^2, HIV subtype A6/A1, and known rilpivirine-associated RAMs. §Non-standard ART regimens included: lamivudine, rilpivirine, and dolutegravir (n=1), darunavir, raltegravir, and cobicistat (n=1), darunavir, raltegravir, and ritonavir (n=1), darunavir and ritonavir (n=1), dolutegravir monotherapy (n=1), rilpivirine mono-therapy (n=1), rilpivirine, darunavir, dolutegravir, and ritonavir (n=1), tenofovir alafenamide, emtricitabine, darunavir, dolutegravir, and cobicistat (n=4), tenofovir alafenamide, emtricitabine, darunavir, elvitegravir, and cobicistat (n=1), tenofovir alafenamide, fostemsavir, rilpivirine, and dolutegravir (n=2), tenofovir disoproxil fumarate, emtricitabine, darunavir, raltegravir, and ritonavir (n=1), tenofovir disoproxil fumarate, emtricitabine, efavirenz, and raltegravir (n=1), and zidovudine, lamivudine, and nelfinavir (n=1). ¶A blip was defined as a viral load between 50 and 199 copies per mL, and these data are presented as the number of blips in the 2 years before the start of follow-up.

Table 1: **Sociodemographic and health-related characteristics at the start of follow-up**

or more, with or without the detection of cabotegravir or rilpivirine resistance associated mutations, or a one-time plasma HIV RNA of 200 copies per mL or more with cabotegravir or rilpivirine resistance-associated mutations.[22] Because some exposed individuals initiated cabotegravir and rilpivirine as part of participating in a clinical trial, we additionally assessed the loss of virological control solely among individuals who initiated cabotegravir and rilpivirine from June, 2021, and received cabotegravir and rilpivirine during routine care in a sensitivity analysis.

	Exposed		Unexposed	
	Virological failure (n=14)	No virological failure (n=571)	Virological failure (n=29)	No virological failure (n=1141)
Age	42 (36–50)	44 (34–54)	44 (36–53)	46 (36–55)
Gender				
Men	13 (93%)	518 (91%)	23 (79%)	1041 (91%)
Women	0	53 (9%)	6 (21%)	100 (9%)
Transgender women	1 (7%)	0	0	0
Men who have sex with men	9 (64%)	439 (77%)	16 (55%)	887 (78%)
Region of origin				
Netherlands	4 (29%)	320/568 (56%)	9/28 (32%)	710/1134 (63%)
Europe, North America, and Australia	1 (7%)	81 (14%)	3 (10%)	134 (12%)
The Caribbean and Latin America	6 (43%)	87 (15%)	11 (38%)	134 (12%)
Sub-Saharan Africa	2 (14%)	40 (7%)	3 (10%)	83 (7%)
South Asia	0	16 (3%)	0 (0%)	39 (3%)
Other	1 (7%)	24 (4%)	2 (7%)	34 (3%)
HIV subtype A6*	1/6 (17%)	3 (1%)	0	3 (1%)
BMI >30 kg/m²	4 (29%)	87/569 (15%)	6 (21%)	118/1137 (10%)
Known rilpivirine-associated RAMs at baseline†	0	0	0	0
Cumulative number of baseline factors associated with cabotegravir and rilpivirine failure				
1	3 (21%)	90 (16%)	NA	NA
2	1 (7%)	0	NA	NA
3	0	0	NA	NA
ART class during follow-up				
Dual therapy	NA	NA	1 (3%)	175 (15%)
INSTI-based triple	NA	NA	21 (72%)	601 (53%)
NNRTI-based triple	NA	NA	6 (21%)	310 (27%)
PI-based triple	NA	NA	1 (3%)	55 (5%)
Years since start of ART	7·6 (5·2–13·1)	8·7 (5·8–13·3)	9·9 (6·2–14·5)	8·7 (5·8–13·2)
Nadir CD4 cell count, cells per µL	265 (110–335)	320 (200–513)	298 (225–427)	330 (203–510)
CD4 cell count at the start of follow-up, cells per µL	744 (440–810)	736 (570–930)	736 (440–960)	772 (590–988)
Blips before the start follow-up‡	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)

Data are n (%) or median (IQR). Data are missing for region of birth (n=11), BMI (n=6), years since the start of ART (n=5), nadir CD4 cell count (n=78), CD4 cell count at the start of follow-up (n=54), and blips before the start of follow-up (n=3). ART=antiretroviral therapy. INSTI=integrase strand transfer inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. RAM=resistance-associated mutation. Information on HIV subtype A6 was available for 260 exposed and 543 unexposed individuals. †Defined as high-level resistance to rilpivirine. Information on rilpivirine-associated RAMs before the start of follow-up was available for 234 exposed and 487 unexposed individuals. The resistance score was calculated using the Stanford algorithm. ‡A blip was defined as a viral load between 50 and 199 copies per mL, and these data are presented as the number of blips in the 2 years before the start of follow-up.

Table 2: **Sociodemographic and health-related characteristics at the start of follow-up for exposed and unexposed individuals with and without a virological failure**

For exposed individuals, we calculated the timing of injections during follow-up and the number of injections administered outside the treatment window. All exposed individuals who did a period of oral bridging using oral cabotegravir and rilpivirine, or who temporarily switched to another regimen, were excluded for the timepoints during which they used an oral regimen.

To assess the potential risk factors for loss of virological control, we modelled the probability of a loss of virological control using a parametric proportional hazards model with a piecewise exponential survival function, stratified by cohort (ie, exposed individuals and individuals who previously had virological failure or were viraemic at cabotegravir and rilpivirine initiation). We included covariates to the model to obtain the hazard ratio (HR) and 95% CIs comparing the hazard of loss of virological control across levels of determinants. We tested variable estimates using the Wald's χ^2 test. We constructed a multivariable model by including all determinants with a p value of less than 0·2 in a univariable analysis. All statistical analyses were performed using STATA (version 15.1) or R (version 4.2.1).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the primary analysis, 585 individuals initiated cabotegravir and rilpivirine treatment between Feb 27, 2018, and Aug 17, 2023, and had at least one clinical visit after baseline. These exposed individuals were matched to 1170 unexposed individuals, of whom 622 (53%) used an INSTI-based triple regimen, 316 (27%) an NNRTI-based triple regimen, 176 (15%) dual therapy (dolutegravir and lamivudine n=156, dolutegravir and boosted darunavir n=14, and rilpivirine and dolutegravir n=6), and 56 (5%) a boosted protease inhibitor-based triple regimen. As shown in table 1, exposed individuals were younger than those unexposed (p=0·033) and had lower CD4 cell counts at baseline (p=0·013). Furthermore, exposed individuals more often had a BMI of more than 30 kg/m² (p=0·0030). Information on rilpivirine-associated RAMs before baseline was available for 255 (44%) exposed individuals. None had any known previous RAM associated with high-level resistance (ie, a level of resistance similar to that observed in viruses with the highest levels of reduced in vitro susceptibility or in viruses that have little or no virological response to that antiretroviral treatment) to rilpivirine or cabotegravir, but seven had RAMs that also occurred as polymorphisms associated with low-level (RAMs associated with a reduction in in vitro antiretroviral therapy susceptibility or a suboptimal virological response to antiretroviral treatment) rilpivirine resistance (all Glu138Ala and Glu138Gly). 551 (94%) exposed individuals used an oral lead-in.

Median follow-up time was 1·3 years (IQR 0·9 to 1·7): 1·3 years (0·9 to 1·8) for exposed and 1·3 years (1·0 to 1·6) for unexposed individuals (p=0·498). 14 exposed (2%) and 29 unexposed (2%) individuals had a loss of virological control during follow-up (p=0·913; table 2). The cumulative probability of loss of virological control is shown in figure 1. There was no difference in the risk of loss of virological control between exposed and unexposed individuals (HR=0·93, 95% CI 0·49 to 1·77). The RMST until loss of virological control was 2·964 years (95% CI 2·296 to 3·002) for exposed individuals and 2·938 years (2·898 to 2·977) for unexposed individuals (difference=0·026, 95% CI –0·029 to –0·080; appendix p 2). In a sensitivity analysis including the 545 exposed (and 1090 unexposed individuals) who initiated cabotegravir and rilpivirine from June, 2021, onwards during routine care, 13 (2%) exposed and 24 (2%) unexposed individuals had a loss of virological control (p=0·814). The RMST until loss of virological control was 1·619 (95% CI 1·605 to 1·633) for exposed individuals and 1·622 (1·613 to 1·632) for unexposed individuals (difference=0·003, 95% CI –0·020 to 0·013).

Of the 14 exposed individuals who had a loss of virological control during follow-up, 13 were men and one was a transgender woman (table 2; appendix pp 4–5). BMI was more than 30 kg/m² at baseline for four (29%) of the 14 individuals and between 25 and 30 kg/m² for six individuals (43%). Longer needles were used for two of the individuals with a BMI of more than 30 kg/m² at baseline; for one individual, longer needles were used later during the treatment phase due to a weight increase. One person (individual number 13; figure 2) with loss of virological control had both HIV subtype A6 and a BMI of more than 30 kg/m² at cabotegravir and rilpivirine initiation (appendix pp 4–5). Time until loss of virological control ranged between 86 and 1173 days after start of follow-up. All cabotegravir and rilpivirine injections were given within the appropriate time window. Seven individuals re-suppressed spontaneously without change in ART (figure 2). Two of these seven individuals re-suppressed spontaneously, but later switched ART due to an adverse event regarded as unrelated to cabotegravir and rilpivirine by the treating physician. The median viral load at moment of loss of virological control for these seven individuals was 331 copies per mL (IQR 215–600); in none of these individuals was a genotypic resistance test performed by the treating physician.

The other seven individuals switched ART; six had confirmed virological failure with INSTI or NNRTI resistance-associated mutations, or both. For one individual with a one-time viral load of 1173 copies per mL, two attempts to perform a genotypic resistance test at different laboratories resulted in no PCR product that could be sequenced. Treatment in this individual was intensified with tenofovir alafenamide, emtricitabine, cobicistat, and darunavir. In these seven individuals, the median HIV-1 RNA at first virological failure was 1471 copies per mL (IQR 334 to 15 000). Cabotegravir and rilpivirine plasma concentrations at time of loss of virological control were available for four exposed individuals. Both cabotegravir and rilpivirine concentrations were less than their first quartile (ie, less than 1·120 mg/L and 0·032 mg/L for cabotegravir and rilpivirine, respectively)[16] for one exposed individual (0·910 mg/L cabotegravir and 0·026 mg/L rilpivirine); one person had too low rilpivirine concentrations (0·005 mg/L), whereas their cabotegravir concentration was normal (2·500 mg/L). Among the 29 unexposed individuals who had a loss of virological control, none switched ART. 19 individuals resuppressed spontaneously within the study period, two individuals resuppressed but became viraemic again, three individuals had two subsequent HIV RNA measurements of 200 copies per mL or more, and for five individuals, additional HIV RNA measurements were not yet available. No information on treatment adherence was available. For three unexposed individuals, a sequence was available at the time of loss of virological control; none had RAMs.

57 (10%) of 571 exposed and 136 (12%) of 1141 unexposed individuals without a loss of virological control discontinued ART. Adverse events were the most commonly reported reason to discontinue cabotegravir and rilpivirine (n=28 for exposed, n=48 for unexposed; appendix p 3). Two individuals discontinued cabotegravir and rilpivirine due to pain at the injection site.

1771 injections were administered to 485 exposed individuals for whom the exact date of administration was registered (figure 3). The exact date of administration was not recorded for 100 individuals. Injections were given a median of 2 days before the scheduled injection date (IQR –4 to 1 days). Most injections (n=1666; 94%)

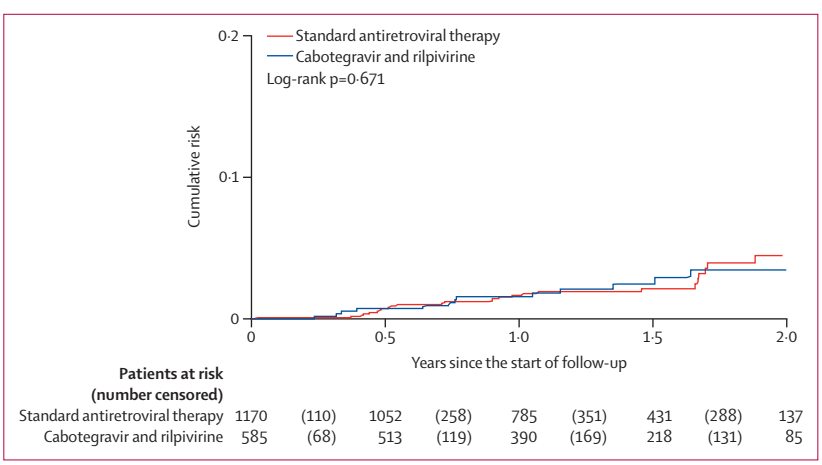
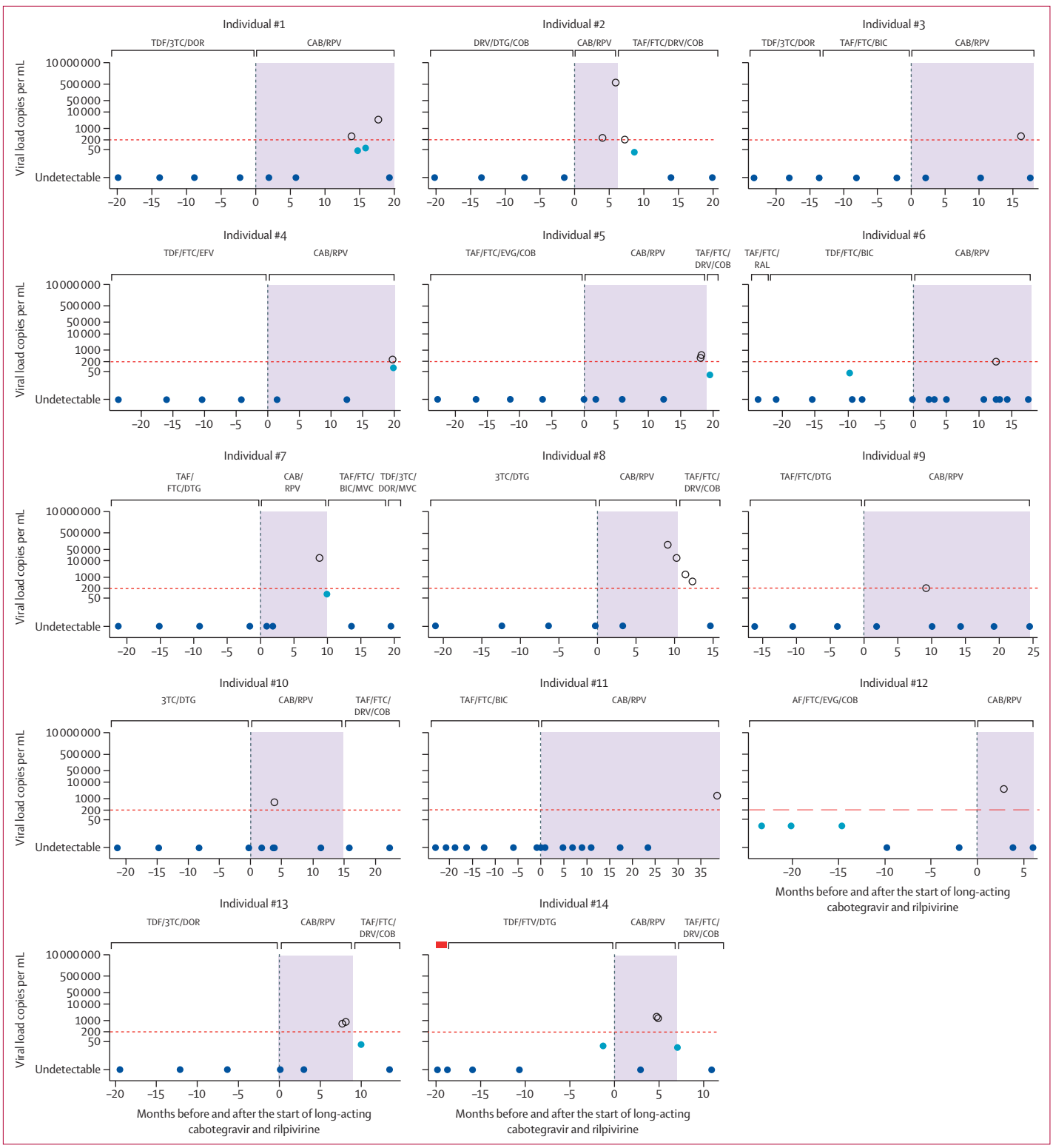


Figure 1: **Estimated cumulative risk of loss of virological control among patients using long-acting injectable cabotegravir and rilpivirine and patients using a standard antiretroviral therapy**
The number in the patient at risk table at each timepoint indicates the total number of patients still at a risk for loss of virological control from that point in time (ie, the patients who were not censored or who did not have a loss of virological control before that timepoint). The number between brackets indicates the number of patients with a loss of virological control between two timepoints. Of note, four events of loss of virological control among one exposed individual and three unexposed individuals occurred after 2 years of follow-up, and these events are thus not visualised in the graph.

were administered within the appropriate time window (±7 days of the scheduled injection date). 25 (1·4%) injections were administered too early (>7 days before the scheduled injection date), and 80 (4·5%) were administered too late (>7 days after the scheduled injection date).



In our secondary analysis, 105 individuals who had previously had virological failure or had a detectable viral load at cabotegravir and rilpivirine initiation between July 1, 2016, and Aug 17, 2023, were assessed. The median age was 43 (IQR 35 to 53) and 57 (54%) were men who have sex with men (table 1). One (2%) of 59 individuals with data available had HIV-1 subtype A6, 13 (15%) of 84 had a BMI of more than 30 kg/m², and four (7%) of 59 had known rilpivirine resistance-associated mutations at start of cabotegravir and rilpivirine treatment (one had a Tyr188Leu mutation, two had a Gly190Ala mutation, and one had a Lys101Glu mutation). One (1%) individual had more than one baseline factor associated with cabotegravir and rilpivirine failure. 13 individuals (13%) of 102 had a HIV-1 RNA between 50 and 199 copies per mL and five (5%) had an HIV-1 RNA of more than 200 copies per mL before starting cabotegravir and rilpivirine treatment. 90 (86%) individuals used an oral lead-in.

The median follow-up time was 1·4 years (IQR 0·8 to 1·8). Nine (9%) of 105 individuals, of whom seven were women, had a loss of virological control during follow-up (figure 4; appendix p 6, 7). Three individuals had a BMI of more than 30 kg/m² at start of follow-up, but longer needles were not used. None had a HIV-1 A6 subtype or pre-existing RAMs associated with rilpivirine resistance. Time until loss of virological control ranged between 18 and 678 days. HIV-1 RNA at the moment of loss of virological control ranged between 200 and 8 310 000 copies per mL. All cabotegravir and rilpivirine injections for the individuals who had a loss of virological control were given within the appropriate time window. Two individuals re-suppressed without a change in ART, of whom one later switched ART due to a an indication that they wanted to become pregnant. Seven additional individuals switched ART after a loss of virological control. Five individuals had confirmed virological failure with new RAMs associated with INSTI or NNRTI resistance. Cabotegravir and rilpivirine plasma concentrations at time of loss of virological control were available for three and five individuals, respectively. Cabotegravir concentrations were less than the first quartile in all three individuals (0·42 mg/L, 0·84 mg/L, and 0·95 mg/L); rilpivirine concentrations were more than the first quartile for all individuals.

Four (4%) of 96 individuals without a loss of virological control discontinued long-acting cabotegravir and rilpivirine. Adverse events (weight gain, fatigue, and nausea) were reported by three individuals (3%). For one individual (1%), the reason for discontinuation was a hepatitis B reactivation.

We found no risk factors for the loss of virological control in the cohort of exposed individuals (appendix p 8). For the individuals who previously had a virological failure or had a detectable viral load, or both, at cabotegravir and rilpivirine initiation, being female (adjusted HR 15·11, 95% CI 1·85–123·07) and having a previous AIDS diagnosis (4·32, 1·03–18·09) increased the risk of loss of virological control, although uncertainty was high (ie, very broad CIs).

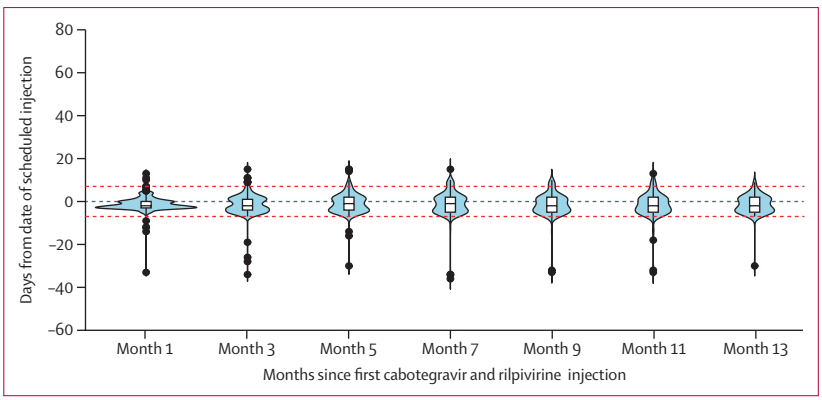


Figure 3: **Timing of cabotegravir and rilpivirine injections after the first cabotegravir and rilpivirine injection**
The boxplot indicates the median, IQR, and range of the number of days from the planned date of the first injection. The violin plot indicates the density of patients who received an injection a specific number of days from the planned date. The dashed red line indicates the 7 day window.

Figure 2: **Viral load before and after the start of long-acting cabotegravir and rilpivirine for exposed individuals**
0 indicates the first viral load measurement after the start of long-acting cabotegravir and rilpivirine; negative months indicate the months before the start of long-acting cabotegravir and rilpivirine. The light purple shading indicates the period during which long-acting cabotegravir and rilpivirine was used. The antiretroviral therapy regimen used during each period is indicated above the graph. The red dashed line indicates a viral load of 200 copies per mL. Red blocks mean no antiretroviral therapy use. The y-axis is on a logarithmic scale. RAMs were detected after loss of virological control for individual number 2 (integrase inhibitor Asn155His, reverse transcriptase Lys101Glu, Glu138Lys, and Met230Leu), individual number 5 (reverse transcriptase Tyr188Leu), individual number 7 (integrase inhibitor Gln148Arg, reverse transcriptase Lys101Glu and Glu138Lys), individual number 8 (integrase inhibitor Gly140Cys and Gly140Ser, and Gln148Arg, reverse transcriptase Lys101Glu), individual number 13 (integrase inhibitor Asn155Ser reverse transcriptase Glu138Lys), and individual number 14 (integrase inhibitor Leu74Ile and Val165Ile, reverse transcriptase Tyr181Cys and His221Tyr). Individual number 11 switched to TAF, FTC, DRV, and COB after loss of virological control but still received a cabotegravir and rilpivirine injection shortly after switching. 3TC=lamivudine. BIC=bictegravir. CAB=cabotegravir. COB=cobicistat. DOR=doravirine. DRV=darunavir. DTG=dolutegravir. EFV=efavirenz. FTC=emtricitabine. MVC=maraviroc. RAL=raltegravir. RAM=resistance-associated mutation. RPV=rilpivirine. TAF=tenofovir alafenamide. TDF= tenofovir disoproxil fumarate.

Discussion

In this nationwide prospective cohort study, we showed that the risk of loss of virological control after the initiation of cabotegravir and rilpivirine among individuals without previous treatment failure was 2% after a median follow-up of 1·3 years, which was similar to individuals on a standard oral ART regimen. Among those who had a loss of virological control, six exposed individuals (1%) had confirmed virological failure, with major INSTI and NNRTI RAMs at the time of a loss of virological control. In comparison, none of the unexposed individuals switched ART or had INSTI or NNRTI RAMs after virological failure. Among the 105 individuals who did previously have a virological failure or had a

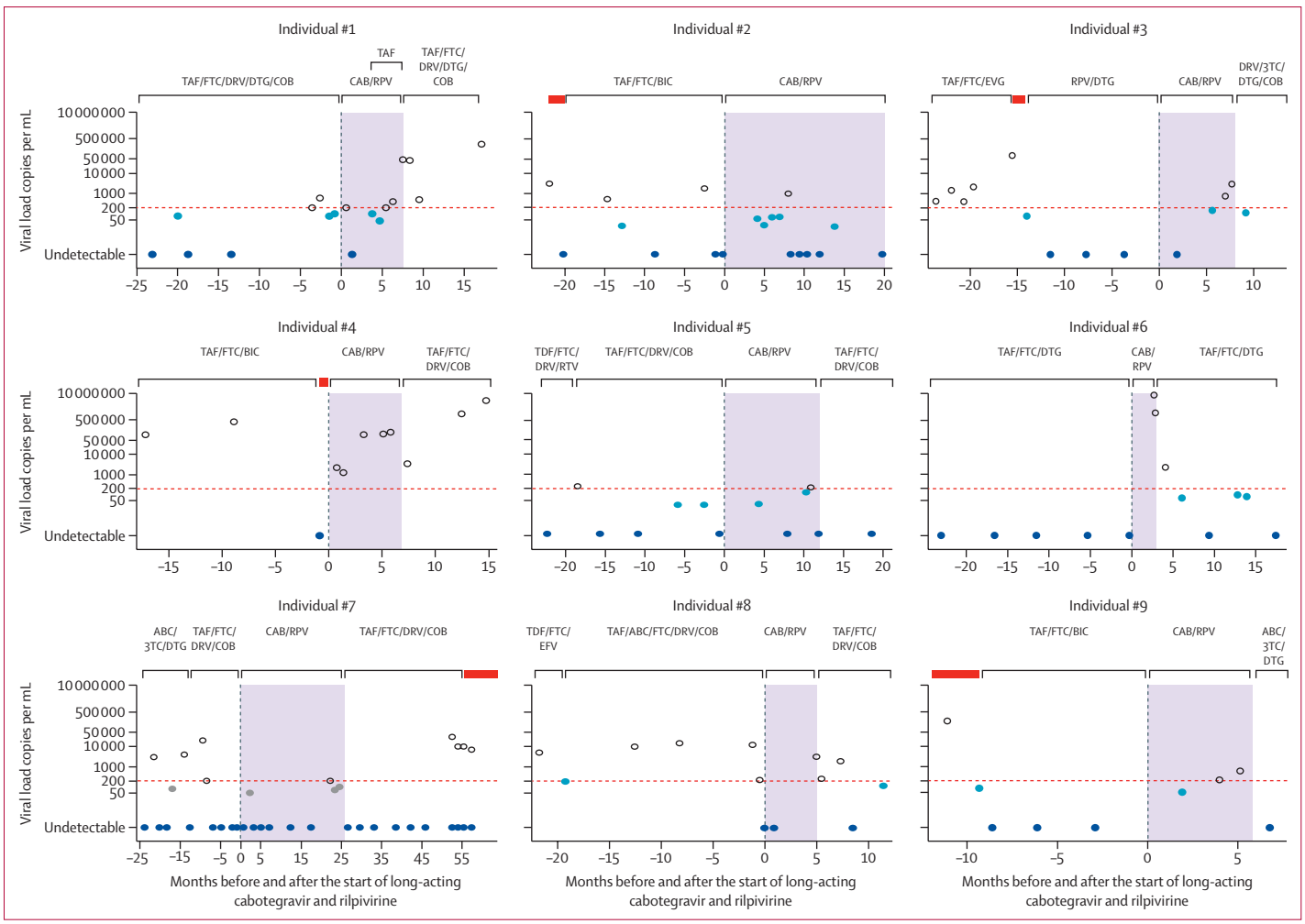


Figure 4: **Viral load before and after the start of long-acting cabotegravir and rilpivirine among individuals who had a virological failure or were viraemic before start of cabotegravir and rilpivirine**
0 indicates the first viral load measurement after the start of long-acting cabotegravir and rilpivirine; negative months indicate the months before start of long-acting cabotegravir and rilpivirine. The light purple shading indicates the period during which long-acting cabotegravir and rilpivirine was used. The antiretroviral therapy regimen used during each period is indicated above the graph. The red dashed line indicates a viral load of 200 copies per mL. The red bars indicate no antiretroviral therapy use. The y-axis is on a logarithmic scale. RAMs were detected after virological failure for individual number 1 (integrase inhibitor Asn155His), individual number 3 (integrase inhibitor Gln148Arg reverse transcriptase Tyr181Cys), individual number 4 (reverse transcriptase Glu138Lys), individual number 6 (reverse transcriptase Lys101Glu, Val179Asp, Tyr181Cys, and Val189Ile), and individual number 9 (reverse transcriptase Lys101Glu). 3TC=lamivudine. ABC=abacavir. BIC=bictegravir. CAB=cabotegravir. COB=cobicistat. DOR=doravirine. DRV=darunavir. DTG=dolutegravir. EFV=efavirenz. FTC=emtricitabine. MVC=maraviroc. RAL=raltegravir. RAM=resistance-associated mutation. RPV=rilpivirine. RTV=ritonavir. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate.

non-supressed HIV-1 RNA, or both, at start of cabotegravir and rilpivirine treatment, the risk of the a loss of virological control was high (nine [9%] of 105), of whom 56% had newly developed INSTI or NNRTI resistance. 57 (10%) exposed individuals and four (4%) individuals in secondary analysis discontinued cabotegravir and rilpivirine for reasons other than virological failure. The 10% discontinuation among exposed individuals was slightly higher than the 8–9% previously reported in clinical trials,[8,9] and could be related to the inclusion of highly motivated early adapters (ie, individuals who are eager to try a new product more often participate in clinical trials) in the trials. However, adverse events were the most common reason for discontinuation of cabotegravir and rilpivirine.

We reported a slightly lower risk of confirmed virological failure compared with previous clinical trials and a large Swiss observational study.[14,15] Additionally, similar to clinical trials, we found the effectiveness of cabotegravir and rilpivirine to be similar to that of a standard oral ART in individuals with no previous history of virological failure.[8,9] 14 exposed individuals did have a loss of virological control. Insufficient drug concentrations of rilpivirine or cabotegravir might explain these occurrences, but unfortunately cabotegravir and rilpivirine drug concentrations were only available for four exposed individuals with a loss of virological control. For two individuals, rilpivirine concentrations were too low, and for one individual, cabotegravir concentration was also too low.[16] An explanation for low plasma concentrations

could be related to the injection technique or needle length. For individuals with a BMI of 30 kg/m² or more, longer needles are advised,[21] but longer needles were only used in three of four of individuals with a BMI of 30 kg/m² or more at cabotegravir and rilpivirine initiation.

Among individuals who had a previous virological failure or had a detectable HIV-1 RNA, or both, at the start of cabotegravir and rilpivirine treatment, the risk of a loss of virological control was much higher, despite the adequate timing of injections. Three individuals had one additional pre-existing risk factor (ie, a BMI of ≥30 kg/m²) associated with an increased risk of failure.[14] All but one of these individuals had virological blips or higher viral loads, or both, in the 24 months preceding the initiation of cabotegravir and rilpivirine. One individual had a high HIV-1 RNA at time of a loss of virological control (8 310 000 copies per mL). This result could suggest the partial absence of drug pressure at the time of a loss of virological control, reflected by the low cabotegravir concentration, and perhaps additionally the suboptimal exposure to rilpivirine given that the rilpivirine plasma concentration was just above the first quartile. Notably, according to the medical records, all injections were given on time, although an administration error cannot be excluded and might have occurred. We also found that being female was associated with an increased risk of a loss of virological control among individuals who had a previous virological failure or had a detectable HIV-1 RNA, or both, at the start of cabotegravir and rilpivirine. This finding was unexpected and, although highly speculative, could be related to more subcutaneous fat in the gluteal–femoral region compared with men,[26] possibly leading to more frequent suboptimal intramuscular administration of cabotegravir and rilpivirine. In general, more careful consideration before prescribing cabotegravir and rilpivirine is needed in individuals with a history of a virological failure. However, cabotegravir and rilpivirine might offer relief to daily pill taking,[3,6,27] and could be of benefit for individuals with adherence challenges, because continuing oral ART when adherence is low is associated with high rates of virological failure.[18,28,29]

In total, 11 individuals had confirmed virological failure with both INSTI and NNRTI RAMs. Notably, NNRTI (Lys101Glu) and INSTI (Asn155His) RAMs were also found in individuals with low HIV-1 RNA levels at the time of a loss of virological control. The loss of susceptibility to preferred treatment options in two major ART classes might justifiably cause concerns among health-care workers and people with HIV, because virological failure on oral ART regimens does not readily lead to a similar loss in treatment options.[30] We found that nine individuals re-suppressed spontaneously. Cabotegravir and rilpivirine concentrations were potentially low in these individuals at the end of a dosing interval, but they received a subsequent dose of cabotegravir and rilpivirine before the virus had sufficient time to replicate and subsequently select INSTI or NNRTI RAMs, or both. An increased monitoring frequency of HIV RNA could lead to more timely detection of virological failure and might avert RAM selection. However, given the low risk of RAM selection on cabotegravir and rilpivirine, increasing the monitoring frequency will need to be assessed for feasibility.

A major strength of our study is the use of a comprehensive prospective cohort consisting of more than 98% of all individuals receiving HIV care in the Netherlands. This method provides a unique surveillance tool for the effectiveness of novel ART. Nevertheless, this study is not without limitations. First, some individuals using cabotegravir and rilpivirine were not included in our database. Some of these individuals had a virological failure,[16] thus virological failure due to cabotegravir and rilpivirine could be different than reported here. Second, given the routine clinical nature of our cohort, viral load was measured at longer intervals and the decisions to switch treatment were not standardised. Therefore, we were unable to confirm the virological failure for all individuals who had a loss of virological control. Third, due to the heterogeneity of individuals included in the secondary analysis with respect to previous treatment regimens and type of pre-existing RAMs, matching these individuals to those unexposed was not feasible. Therefore, we are unable to make any conclusions related to the risk of a loss of virological control compared with unexposed individuals for this cohort. Last, our results might not be generalisable to the broader population of individuals with HIV. More than 90% of exposed individuals and 70% of individuals in the secondary cohort were male and more than half of both groups were born in the Netherlands. Moreover, adherence to the treatment schedule was very high, with 94% of injections given within the appropriate time window, which probably contributed to the high level of virological success.

In conclusion, switching to cabotegravir and rilpivirine was not associated with a higher risk of a loss of virological control compared with standard antiretroviral therapy among individuals without previous treatment failure. The risk of a loss of virological control was considerably higher among individuals with previous treatment failure, especially when compared with individuals without previous virological failure. Initiating cabotegravir and rilpivirine in these individuals might therefore only be beneficial when adherence problems to oral ART indicate an even higher risk of virological failure than switching to cabotegravir and rilpivirine. In 11 individuals, INSTI or NNRTI RAMs, or both, were documented, thereby limiting treatment options.

Contributors

VWJ, FWNMW, and MvdV conceptualised and designed this study. VWJ, AB, and FWNMW accessed and verified the data. VWJ, AB, and FWNMW were involved in the data management and analysis. VWJ, FWMNW, AB, and MvdV were involved with interpretation of the data. VWJ drafted the manuscript. All authors read and approved the

final manuscript. MvdV had final responsibility for the decision to submit for publication.

Declaration of interests

FWNMW received fees for advisory boards from Gilead Sciences and ViiV Healthcare. AB received speaker's fees from Gilead Sciences. MvdV received unrestricted research grants and fees for participation in advisory boards from Gilead Sciences, MSD, and ViiV Healthcare, all paid to his institution. AMJW has received unrestricted research grants from Gilead Sciences; fees for participation in advisory boards from Gilead Sciences, Merck, and ViiV Healthcare/GSK; and received drug level kits from ARK Diagnostics, all paid to her institution. REM received unrestricted research grants from Gilead Sciences; fees for participation in advisory boards from Gilead Sciences and ViiV Healthcare; and fees for workshops and lectures for ViiV Healthcare, all paid to her institution. All other authors declare no competing interests.

Data sharing

The ATHENA cohort data used in this study are available upon reasonable request. Requests for data access can be made to: hiv.monitoring@amsterdamumc.nl. These will be reviewed on a case-by-case basis, given that the data underlying this study contain sensitive information. Statistical information or data for separate research purposes from the ATHENA cohort can be requested by submitting a research proposal to Stichting HIV Monitoring (https://www.hiv-monitoring.nl/english/research/research-projects/). The proposal will undergo review by representatives of Stichting HIV Monitoring for evaluation of scientific value, relevance of the study, design, and feasibility, statistical power, and overlap with existing projects.

Acknowledgments

The ATHENA Cohort is managed by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare, and Sport through the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment. We thank all participants in the ATHENA cohort and the coordinating treating physicians at the HIV treatment centres. We thank the data collecting staff and central coordinating staff at the HIV Monitoring Foundation (managing the ATHENA cohort).

References

1 van Bilsen WPH, Zimmermann HML, Boyd A, Davidovich U. Burden of living with HIV among men who have sex with men: a mixed-methods study. *Lancet HIV* 2020; **7:** e835–43.
2 Katz IT, Ryu AE, Onuegbu AG, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. *J Int AIDS Soc* 2013; **16:** 18640.
3 de Los Rios P, Okoli C, Castellanos E, et al. Physical, emotional, and psychosocial challenges associated with daily dosing of HIV medications and their impact on indicators of quality of life: findings from the positive perspectives study. *AIDS Behav* 2021; **25:** 961–72.
4 Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to antiretroviral therapy and virologic failure: a meta-analysis. *Medicine (Baltimore)* 2016; **95:** e3361.
5 Rai S, Mahapatra B, Sircar S, et al. Adherence to antiretroviral therapy and its effect on survival of HIV-infected individuals in Jharkhand, India. *PLoS One* 2013; **8:** e66860.
6 Dandachi D, Dang BN, Lucari B, Swindells S, Giordano TP. Acceptability and preferences for long-acting antiretroviral formulations among people with HIV infection. *AIDS Care* 2021; **33:** 801–09.
7 Akinwunmi B, Buchenberger D, Scherzer J, et al. Factors associated with interest in a long-acting HIV regimen: perspectives of people living with HIV and healthcare providers in four European countries. *Sex Transm Infect* 2021; **97:** 566–73.
8 Swindells S, Andrade-Villanueva J-F, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med* 2020; **382:** 1112–23.
9 Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med* 2020; **382:** 1124–35.
10 Rizzardini G, Overton ET, Orkin C, et al. Long-acting injectable cabotegravir + rilpivirine for HIV maintenance therapy: week 48 pooled analysis of phase 3 ATLAS and FLAIR trials. *J Acquir Immune Defic Syndr* 2020; **85:** 498–506.
11 Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet* 2021; **396:** 1994–2005.
12 Orkin C, Bernal Morell E, Tan DHS, et al. Initiation of long-acting cabotegravir plus rilpivirine as direct-to-injection or with an oral lead-in in adults with HIV-1 infection: week 124 results of the open-label phase 3 FLAIR study. *Lancet HIV* 2021; **8:** e668–78.
13 Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with Human Immunodeficiency Virus 1 type 1 infection: 152-week results from ATLAS-2M, a randomized, open-label, phase 3b, noninferiority study. *Clin Infect Dis* 2023; **76:** 1646–54.
14 Orkin C, Schapiro JM, Perno CF, et al. Expanded multivariable models to assist patient selection for long-acting cabotegravir + rilpivirine treatment: clinical utility of a combination of patient, drug concentration, and viral factors associated with virologic failure. *Clin Infect Dis* 2023; **77:** 1423–31.
15 Thoueille P, Saldanha SA, Schaller F, et al. Real-world trough concentrations and effectiveness of long-acting cabotegravir and rilpivirine: a multicenter prospective observational study in Switzerland. *Lancet Reg Health Eur* 2023; **36:** 100793.
16 van Welzen BJ, Van Lelyveld SFL, Ter Beest G, et al. Virological failure after switch to long-acting cabotegravir and rilpivirine injectable therapy: an in-depth analysis. *Clin Infect Dis* 2024; **79:** 189–95.
17 Sension MG, Brunet L, Hsu RK, et al. Cabotegravir + rilpivirine long-acting injections for HIV treatment in the US: real world data from the OPERA cohort. *Infect Dis Ther* 2023; **12:** 2807–17.
18 Gandhi M, Hickey M, Imbert E, et al. Demonstration project of long-acting antiretroviral therapy in a diverse population of people with HIV. *Ann Intern Med* 2023; **176:** 969–74.
19 John M, Williams L, Nolan G, Bonnett M, Castley A, Nolan D. Real-world use of long-acting cabotegravir and rilpivirine: 12-month results of the inJectable Antiretroviral therapy feasiBility Study (JABS). *HIV Med* 2024; **25:** 935–45.
20 Boender TS, Smit C, Sighem AV, et al. AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. *BMJ Open* 2018; **8:** e022516.
21 European Medicines Agency. Vocabria. https://www.ema.europa.eu/en/medicines/human/EPAR/vocabria (accessed Jan 12, 2024).
22 Wensing AM, Calvez V, Ceccherini-Silberstein F, et al. 2022 update of the drug resistance mutations in HIV-1. *Top Antivir Med* 2022; **30:** 559–74.
23 Struck D, Lawyer G, Ternes A-M, Schmit J-C, Bercoff DP. COMET: adaptive context-based modeling for ultrafast HIV-1 subtype identification. *Nucleic Acids Research* 2014; **42:** e144-e.
24 Cronin A, Tian L, Uno H. strmst2 and strmst2pw: new commands to compare survival curves using the restricted mean survival time. *Stata J* 2016; **16:** 702–16.
25 Cronin A. STRMST2: Stata module to compare restricted mean survival time. https://ideas.repec.org/c/boc/bocode/s458154.html (accessed Jan 12, 2024).
26 Blaak E. Gender differences in fat metabolism. *Curr Opin Clin Nutr Metab Care* 2001; **4:** 499–502.
27 Kerrigan D, Mantsios A, Gorgolas M, et al. Experiences with long acting injectable ART: a qualitative study among PLHIV participating in a phase II study of cabotegravir + rilpivirine (LATTE-2) in the United States and Spain. *PLoS One* 2018; **13:** e0190487.
28 Ciccullo A, Iannone V, Lombardi F, Borghetti A, Di Giambenedetto S. Letter to the Editor: real-life experience of long-acting cabotegravir–rilpivirine combination in a person living with HIV with detectable viremia: a case report. *AIDS Res Hum Retroviruses* 2024; **40:** 555–56.
29 Rana AI, Bao Y, Zheng L, et al. Long-acting injectable CAB/RPV is superior to oral ART in PWH with adherence challenges: ACTG A5359. CROI, Denver, CO; March, 3-4, 2024 (abstr 212).
30 Armenia D, Santoro MM, Charpentier C, et al. Evaluation of integrase resistance in individuals who failed a regimen containing dolutegravir in French and Italian clinical settings. *J Antimicrob Chemother* 2023; **78:** 1415–22.