A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial

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Summary

Background Intermittent (on 4 days per week) antiretroviral therapy (ART) for patients with HIV-1 might be more convenient, better tolerated, and cheaper than continuous treatment. We aimed to establish the efficacy and safety of a 4-days-on and 3-days-off (intermittent) maintenance regimen versus a standard 7 day (continuous) maintenance regimen.

Methods In a randomised, open-label, multicentre, parallel, non-inferiority trial, we randomly assigned (1:1) adults with HIV-1 infection with a plasma viral load (pVL) of less than 50 copies per mL for more than 12 months and no drug-resistance mutations to either the intermittent regimen or their existing continuous maintenance regimen, with stratification according to third therapeutic agent (protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase-strand transfer inhibitor). Participants were recruited from 59 hospitals throughout France. The main exclusion criteria were CD4 cell count lower than 250 cells per µL and chronic hepatitis B virus infection. The primary endpoint was the proportion of participants in the modified intention-to-treat (mITT) population who started the study strategy presenting treatment success at week 48 (pVL <50 copies per mL without strategy modification), estimated using the US Federal Drug Administration snapshot approach, with a 5% non-inferiority margin. The study was registered with ClinicalTrials.gov (NCT03256422) and EudraCT (2017-000040-17). The trial is now closed.

Findings From Sept 7, 2017, to Jan 22, 2018, 850 potential participants were screened for eligibility. 647 participants were enrolled and randomly assigned (1:1) to either the intermittent or the continuous treatment group. The mITT population included 636 participants (318 per group). At week 48, in the mITT population, treatment success was recorded in 304 (96%) of 318 participants in the intermittent treatment group and 308 (97%) of 318 in the continuous treatment group (adjusted difference –1·3%, 95% CI –4·2 to 1·7). Six (2%) participants in the intermittent treatment group and four (1%) participants in the continuous treatment group had virological failure. Grade 3–4 adverse events were reported in 29 (9%) participants in the intermittent treatment group and 39 (12%) participants in the continuous treatment group (p=0·320). Daily life satisfaction improved in 153 (59%) of 258 participants in the intermittent treatment group versus 19 (7%) of 255 in the continuous treatment group (p<0·0001). ART costs were 43% lower in the intermittent treatment group than in the continuous treatment group (p<0·0001).

Interpretation These findings show the non-inferiority of the treatment strategy of 4-consecutive-days-on and 3-days-off strategy maintenance regimen relative to standard continuous ART triple therapy over 48 weeks. 4 days on and off treatment represents a workable, effective alternative strategy for patients with high adherence to ART, and using a drug combination with a high genetic barrier to resistance.

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Introduction

Antiretroviral therapy (ART) aims to reduce the morbidity and mortality of HIV infection through viral suppression and immune restoration, and to prevent the transmission of the virus between individuals. The success of this strategy depends on preventing both virological failure and the selection of drug-resistance mutations. The 2017 treatment guidelines recommended combination ART with two nucleoside reverse transcriptase inhibitors (NRTI) and a third agent from one of three drug classes, comprising a non-NRTI (NNRTI), boosted protease inhibitor, and an integrase-strand transfer inhibitor

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2000, until Dec 31, 2020, and screened for clinical trial publications, cohort studies, and review articles published in English, using combinations, abbreviations, and variations of the search terms "HIV", "short", "cycles" or "short-cycles", "antiretroviral therapy", "dual therapy", and "treatment simplification". The notion for treatment in HIV for almost 25 years has been that three-drug regimens every day are required to provide adequate virological efficacy and a barrier to emergence of resistance. The first small proof-of-concept studies of short-cycle intermittent antiretroviral maintenance therapy were done in 2001–04, with 7 days on and 7 days off, in adults with suppressed viral load, but this strategy was inferior to continuous treatment in two studies. Subsequently, pilot studies of 7 days on and 7 days off, several maintenance trials of 5 days on and 2 days off, and one randomised trial using 1 day on and 1 day off, mostly with non-nucleoside reverse transcriptase inhibitors (NNRTIs)-based regimens, provided promising results. These findings were confirmed in 2016 in the BREATHER randomised trial involving 199 children, adolescents, and young adults on an efavirenz-based therapy; the rates of unsuccessful treatment were six of 99 patients (5 days on and 2 days off) and seven of 100 patients (continuous) at 48 weeks. A single-arm study of short-cycle therapy with 4 days on and 3 days off showed the maintenance of full viral suppression in 92 adults on various triple-therapy regimens in the open pilot study done by our group. We then did a pilot 4-days-on and 3-days-off maintenance triple-therapy study (ANRS-162 4D) showing the therapeutic success of this strategy in 96% of patients, leading to the design of the present randomised ANRS 170 QUATUOR study. Other approaches of simplification have been evaluated and approved, including the development of two drugs per overall survival regimen for maintenance therapy, and more recently long-acting cabotegravir and rilpivirine intramuscular regimens.

Added value of this study

This study is the first prospective multicentre randomised trial to investigate the efficacy and safety of a 4-days-on and 3-days-off (intermittent) maintenance regimen compared with a standard continuous regimen, for 48 weeks, in 636 adults on standard triple-agent combinations, including either NNRTI-based, protease inhibitor-based, or integrase-strand transfer inhibitor (INSTI)-based treatments. The intermittent triple-therapy regimen was non-inferior to the standard continuous triple-therapy regimen in maintaining virological suppression over 48 weeks (adjusted difference –1·3%, 95% CI –4·2% to 1·7%). Six (2%) participants in the intermittent treatment group and four (1%) in the continuous treatment group had virological failure. New drug-resistance mutations occurred in three of six participants in the intermittent treatment group and in one of four participants in the continuous treatment group. We observed no signals of immune activation and no increase in the viral reservoir (total HIV-1 DNA) in the intermittent treatment group. Acceptability and adherence to the maintenance regimen was high, exceeding 90% at each visit, and participants expressed high satisfaction with the short-cycle therapy, leading them to continue with the study regimen after the end of the trial. Unlike other approaches of simplification no new drug was introduced in the QUATUOR trial, in which participants were maintained on a stable regimen for at least 4 months before screening. As expected, the participants in the QUATUOR trial did not, therefore, experience new substantial antiretroviral therapy-related adverse events.

Implications of the available evidence

The non-inferiority shown in the ANRS 170 QUATUOR trial suggests that short-cycle antiretroviral maintenance therapy of 4 consecutive days on and 3 days off with a standard triple-agent combination (mostly based on NNRTIs and INSTIs) is a viable and efficacious option for patients with suppressed viraemia. The strategy leads to a 43% reduction in antiretroviral drug consumption and will benefit patients and communities. As the population with HIV ages, polypharmacy and lifelong cumulative drug exposure might become a more important treatment consideration. 4 days on and 3 days off treatment represents a workable, effective alternative strategy for patients with high adherence to antiretroviral therapy, using a high genetic-barrier drug combination.

(INSTI).[1] However, because treatment is lifelong, there is a risk of poor adherence to treatment, viral escape, and long-term drug toxicity, particularly in older participants with comorbidities. Moreover, less costly antiviral combinations should be considered because of growing economic constraints.[2]

Many studies have examined various strategies for reducing drug exposure in participants with controlled infection on maintenance therapy, including dose reduction,[3] boosted protease-inhibitor monotherapy,[4] dual therapy, such as lamivudine with a boosted protease inhibitor or dolutegravir,[5] and an NNRTI and INSTI, including long-acting cabotegravir and rilpivirine.[6,7] Another approach is based on short-cycle intermittent triple therapy, in which the effective ongoing daily treatment is taken on only 4 consecutive days or 5 consecutive days per week. This strategy has the advantage of substantially decreasing health-care costs, in addition to drug exposure. After pilot studies that investigated 7 days on treatment and 7 days off treatment, several 5 days on and 2 days off maintenance trials mostly with NNRTI-based regimens, and one randomised clinical trial on the efficacy of fixed-dose efavirenz, tenofovir, and emtricitabine on alternate days, provided

promising results.[8–12] The observed success rate of a triple-therapy maintenance regimen involving 4 days on therapy and 3 consecutive days off therapy in Leibowitch's retrospective study[13] led us to do a prospective multicentre 4-days-on and 3-days-off pilot study in participants on a triple-therapy regimen based on an NNRTI or boosted protease inhibitor, with 96% treatment success after 48 weeks.[14] For confirmation of the efficacy of the 4-days-on and 3-days-off strategy in terms of viral success, safety, adherence, and quality of life, we did a randomised, non-inferiority trial (ANRS-170 QUATUOR) to compare this short-cycle intermittent strategy with standard daily continuous treatment with the most widely used ART regimens, including INSTI-based and NNRTI-based regimens, over 48 weeks.

Methods

Study design and participants

ANRS-170 QUATUOR was a randomised, parallel, open-label, multicentre, non-inferiority trial done at 59 hospitals throughout France. Participants received either ART triple therapy on 4 consecutive days per week (either Friday to Sunday or Saturday to Monday, intermittent), or maintained their daily intake (7 days, continuous), for 48 weeks. At week 48, all participants on standard continuous triple therapy with virological success had their treatment switched to the intermittent strategy, and all participants were followed for an additional 48 weeks, until week 96.

The ART regimens permitted at inclusion were: tenofovir disoproxil fumarate, tenofovir alafenamide, emtricitabine, abacavir, and lamivudine for NRTI; lopinavir–ritonavir, darunavir–ritonavir, and atazanavir–ritonavir for protease inhibitor; efavirenz, rilpivirine, and etravirine for NNRTI; and dolutegravir, elvitegravir–cobicistat, and raltegravir for INSTI.

Adults with HIV-1 infection (aged ≥18 years) on daily triple therapy combining two NRTIs with a protease inhibitor, NNRTI, or INSTI as the third agent, unchanged for at least 4 months, were eligible if they had a plasma viral load (pVL) of less than 50 copies per mL for more than 12 months, and an HIV infection susceptible to all antiretroviral drugs in their ongoing treatment, according to previous plasma RNA or peripheral blood mononuclear cell DNA genotyping done in accordance with the version of the French resistance algorithm available during the inclusion period. Exclusion criteria included: a CD4 count of less than 250 cells per µL; chronic and active viral hepatitis B; chronic and active viral hepatitis C requiring treatment during the study; use of immunotherapy or chemotherapy; treatment for an opportunistic infection; an estimated glomerular filtration rate (eGFR) of up to 60 mL/min; a platelet count of up to 100 000 cells per µL; haemoglobin of up to 10 g/dL; aspartate aminotransferase (AST) or alanine aminotransaminase (ALT) up to three times the upper limit of normal; and women who were pregnant, breastfeeding, or not taking contraception during the study period.

All participants provided written informed consent. The study was approved by the French Sud-Ouest Outre-Mer III ethics committee. The study was registered at ClinicalTrials.gov (NCT03256422) and EudraCT (2017-000040-17).

Randomisation and masking

Eligible individuals were randomly assigned in a 1:1 ratio either to switch to the intermittent strategy or to remain on their existing continuous strategy for 48 weeks. Randomisation was stratified by the third antiretroviral agent class (ie, INSTI, NNRTI, or protease inhibitor). The trial statistician (LA) used a centralised computer-generated randomisation list with a permuted block size of four to assign participants to treatment groups, and was involved in the rest of the unmasked randomised trial. The randomisation list was integrated by the study data manager (JB) in the electronic case-report form. The study design was open label, so neither participants nor investigators were blinded to group allocation.

Procedures

After the screening visit, eligible participants were seen at the baseline visit (week 0), week 4, week 12, and every 12 weeks thereafter until week 48. For participants randomly assigned to the intermittent treatment strategy, samples were collected at all visits, at the end of the 3-days-off treatment period (referred to hereafter as the off period) before participants reinitiated ART, except at week 12 and week 36, when samples were collected on the third or fourth day of treatment (the 4 days of treatment per week are hereafter referred to as the on period) to compare drug concentrations during the on-drug period with those during the off-drug period. Other procedures are described in the appendix (p 1).

Outcomes

The primary endpoint for efficacy was the proportion of participants in the modified intention-to-treat (mITT) population (all the randomly assigned participants who started treatment strategy) for whom treatment was successful at week 48, as shown by a pVL of less than 50 copies per mL, with no changes to the treatment strategy, assessed with the US Food and Drug Administration (FDA) snapshot approach.[15] All instances of study follow-up discontinuation were considered as the treatment being unsuccessful, regardless of the reason for discontinuation. Given the non-inferiority design, we also did an efficacy analysis in the per-protocol population. This population included all the participants from the mITT population except those who discontinued treatment strategy for reasons other than virological failure, adverse events, or death, and those who did not fulfil the inclusion criteria or did not adhere to the strategy to which they were randomly assigned for more than 10% of the total study duration.

For more on the **French resistance algorithm** see https://hivfrenchresistance.org/

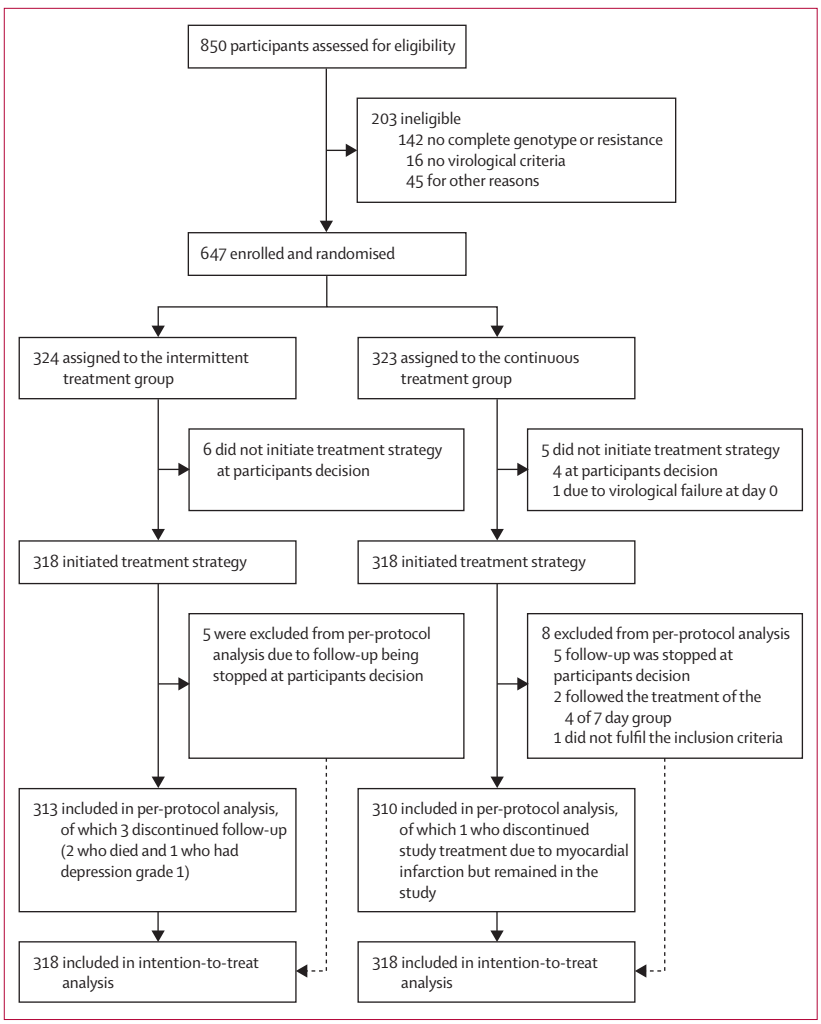

Figure 1: **Study flowchart**
Intermittent treatment=4 days on and 3 day off.

We also did an efficacy analysis on the ITT population (all randomly assigned participants) by considering those who never started the study strategy as having an unsuccessful treatment using the FDA snapshot algorithm.

The secondary endpoints for efficacy were: the proportion of participants in the mITT population with a pVL of more than 50 copies per mL, confirmed within 4 weeks (ie, virological failure), during the 48 weeks of the study between the two groups and during the 96 weeks only in participants with the intermittent strategy from baseline to week 96; incidence of genotypic resistance, assessed following the second pVL test for which pVL was more than 50 copies per mL; the proportion of participants with virological failure at week 48 in the mITT population in subgroups defined according to baseline third-agent class; the incidence of viral blips in the mITT population; and the changes in CD4 and CD8 T-cell concentrations and in the CD4:CD8 ratio in the mITT population.

The secondary endpoints for safety analysis at week 48 and week 96 in the mITT population were: incidence of adverse events, grade 3–4 adverse events, drug-related grade 3–4 adverse events, and death; the proportion of participants discontinuing treatment because of adverse events; the changes in fasting lipid concentrations and glycaemia; the change in AST and ALT concentrations and eGFR calculated with the Chronic Kidney Disease Epidemiology Collaboration protease inhibitor equation. The other secondary endpoints are described in the appendix (p 2).

Statistical analysis

The estimated sample size of 320 participants per treatment group (640 in total) was based on a power of 80%, an α risk of 2·5% in one-tailed tests (α=0·05 in two-tailed tests), a non-inferiority margin of –5% for treatment success, and an assumed true response rate of 95% for both the intermittent and continuous strategies. A non-inferiority margin of 5% was chosen to ensure preservation of treatment effect in those assigned to the intermittent treatment group.

We used Cochran-Mantel-Haenszel tests to assess the difference between treatments in the percentage of participants with treatment success (ie, response rate in the intermittent treatment group minus the response rate in the continuous treatment group) adjusted for baseline third ART agent class (ie, INSTI, NNRTI, or protease inhibitor) to account for the stratification of the randomisation on this variable. The intermittent strategy was considered non-inferior to the continuous strategy if the lower limit of the 95% CI was higher than –5% for both the mITT and per-protocol analyses.

We also calculated the difference in treatment efficacy between the two groups by measuring the difference in the percentage of participants with virological failure (ie, failure rate in the intermittent treatment group minus the failure rate in the continuous treatment group) adjusted for the stratification factor, with a non-inferiority margin of 4%, consistent with the updated guidelines from the US FDA.[16] Subgroup analyses for virological failure were done to assess consistency of the intervention effect across the subgroups using a logistic regression model. The subgroup variables included the third agent class and several demographic and HIV characteristics. The incidence of viral blips (pVL >50 copies per mL with control pVL ≤50 copies per mL) was compared between treatment groups, using a Poisson regression model.

The changes from baseline to week 48 in all continuous variables used as endpoints were compared between the two groups using non-parametric Mann-Whitney *U* tests. Last observation carried forward was used to fill in missing data. Participants with missing data at baseline were excluded.

Adverse events, especially grade 3 and 4 adverse events, drug-related grade 3 or 4 adverse events, treatment interruption due to adverse events (all grades), and death,

were summarised with descriptive statistics. The incidence rates of these events were compared between the treatment groups with a Poisson regression analysis.

Changes in quality-of-life dimensions were compared between groups using analysis of variance. A multiple imputation using the chained equations approach was used to fill in missing data. Five imputations were chosen. Analyses were run on each of the five datasets and the results were combined with Rubin's rules.

All p values are reported for two-tailed tests with a significance threshold of 0·05. The analyses were done with SAS version 9.4 and Stata SE version 13 for Windows.

Role of the funding source

The Institut National de la Santé et de la Recherche Médicale, Maladies Infectieuses Emergentes sponsored the trial. Following approval of the protocol, Inserm-ANRS-MIE played no further role in the collection, analysis, or interpretation of the data. Inserm-ANRS-MIE reviewed the final manuscript. The French National Health Insurance System provided the study treatments.

Results

Participants were screened for eligibility from Sept 7, 2017, to Jan 22, 2018, and followed up until March 16, 2020. In total, 203 (24%) of the 850 participants screened were not eligible. The reasons for non-inclusion are shown in the appendix (p 4). Of the remaining 647 participants randomly assigned to the intermittent or the continuous treatment group, 636 (98%) participants initiated treatment, and were included in the mITT population: 318 (98%) of 324 in the intermittent treatment group and 318 (98%) of 323 in the continuous treatment group (figure 1).

Baseline characteristics of the participants are shown (table 1). Overall, most (85%) of the participants were men, 67% were men who have sex with men, the median age was 49 years (IQR 41–55), and 15% were born in sub-Saharan Africa. Median duration of HIV RNA suppression (<50 copies per mL) was 5·8 years (IQR 3·3–9·6). ART regimens included an INSTI for 304 participants (48%), an NNRTI for 296 (47%) participants, and a protease inhibitor for 36 (6%) participants. Baseline NRTI backbone consisted of tenofovir disoproxil fumarate plus emtricitabine for 358 (56%) participants, tenofovir alafenamide plus emtricitabine for 104 (16%) participants, and abacavir plus lamivudine for 174 (27%) participants.

Until week 48, 13 participants discontinued follow-up (eight in the intermittent treatment group and five in the continuous treatment group; log-rank p=0·40; appendix p 12). The reasons for discontinuation were death (not related to drug strategy) for two participants in the intermittent treatment group, depression grade 1 for one participant in the intermittent treatment group, and personal reasons for five participants in each group, mostly because of dissatisfaction with the randomisation group (one in the intermittent treatment group *vs* three in the continuous treatment group). One participant in the

	Intermittent treatment group (n=318)	Continuous treatment group (n=318)
Age (years)	50 (41–55)	49 (41–56)
Sex		
Male	270 (85%)	269 (85%)
Female	48 (15%)	49 (15%)
Geographical origin*		
European	237 (75%)	249 (78%)
Sub-Saharan African	47 (15%)	51 (16%)
Other	34 (11%)	18 (6%)
Transmission group		
Men who have sex with men	211 (66%)	214 (67%)
Heterosexuals	96 (30%)	86 (27%)
Other	11 (3%)	18 (6%)
Previous AIDS-defining event	36/317 (11%)	42/318 (13%)
HCV co-infection with anti-HCV antibodies	17 (5%)	27 (8%)
Duration of antiretroviral therapy (years), n=631	6·5 (3·8–11·9)	7·4 (4·2–12·5)
Duration of last ART (months)	25 (12–45)	27 (13–51)
Duration of suppression of HIV viraemia to pVL <50 copies per mL (years), n=612	5·1 (3·0–8·6)	6·5 (3·5–10·3)
Pre-ART HIV pVL $\log_{10}$ (copies per mL), n=576	4·9 (4·3–5·3)	4·7 (4·2–5·3)
CD4 count nadir (cells per µL), n=633	313 (203–422)	289 (189–401)
CD4 count (cells per µL)	693 (532–898)	687 (534– 863)
CD4:CD8 ratio	1·0 (0·8–1·4)	1·1 (0·8–1·4)
NRTI backbone		
Tenofovir disoproxil fumarate + emtricitabine	181 (57%)	177 (56%)
Tenofovir alafenamide + emtricitabine	49 (154%)	55 (17%)
Abacavir + lamivudine	88 (28%)	86 (27%)
INSTI	152 (48%)	152 (48%)
Dolutegravir	73 (23%)	76 (24%)
Elvitegravir–cobicistat	65 (20%)	68 (21%)
Raltegravir	14 (4%)	8 (3%)
NNRTI	148 (47%)	148 (47%)
Efavirenz	24 (8%)	32 (10%)
Etravirine	6 (2%)	6 (2%)
Rilpivirine	118 (37%)	110 (35%)
Protease inhibitor	18 (6%)	18 (6%)
Atazanavir–ritonavir	2 (1%)	4 (1%)
Darunavir–ritonavir	16 (5%)	12 (4%)
Lopinavir–ritonavir	0	2 (1%)

Data are n (%) or median (IQR). Intermittent treatment=4 days on and 3 days off. HCV=hepatitis C virus. pVL=plasma viral load. ART=antiretroviral therapy. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. INSTI=integrase strand transfer inhibitor. *Ethnicity details were not collected.

Table 1: **Baseline characteristics of the participants**

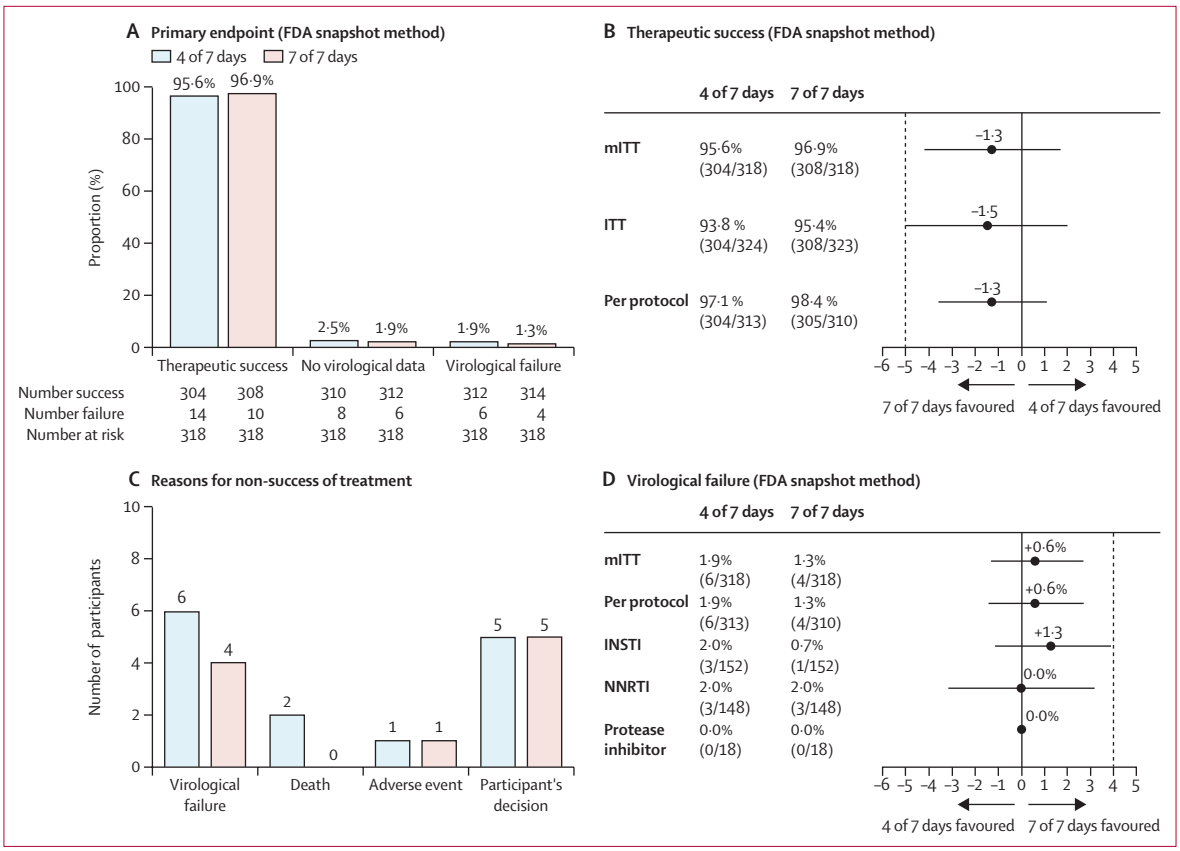

Figure 2: **Primary end point results for therapeutic success and virological failure analysis**
(A) Percentage of participants with HIV RNA of less than 50 copies per mL as established by the FDA snapshot algorithm (therapeutic success). (B) Difference in the percentage of participants with therapeutic success and the associated 95% CI for the mITT, ITT, and per-protocol populations with a predefined non-inferiority margin of –5%. (C) Frequency of the reasons for non-success of treatment. (D) Difference in the percentage of participants with virological failure (two consecutive pVL ≥50 copies per mL) and associated 95% CIs for the mITT and per-protocol populations, and by class of third antiretroviral agent (INSTI, NNRTI, and protease inhibitor) for the mITT population, with a non-inferiority margin of 4%. Dashed lines show non-inferiority margins. FDA=US Food and Drug Administration. INSTI=integrase-strand transfer inhibitor. ITT=intention to treat. mITT=modified intention to treat. NNRTI=non-nucleoside reverse transcriptase inhibitor. pVL=plasma viral load.

continuous treatment group stopped treatment because of myocardial infarction but remained in the study. At least one drug in the baseline regimen was replaced with another from the same class in 65 participants (33 in the intermittent treatment group and 32 in the continuous treatment group; log-rank p=0·86; appendix p 12). The most frequent change was from tenofovir disoproxil fumarate to tenofovir alafenamide (61 participants; 32 in the intermittent treatment group and 29 in the continuous treatment group).

In the mITT population, 304 (96%) of 318 participants in the intermittent treatment group and 308 (97%) of 318 participants in the continuous treatment group maintained pVL lower than 50 copies per mL with no treatment-strategy modification, with an adjusted treatment difference of –1·3% (95% CI –4·2 to 1·7; figure 2A, B), and showed non-inferiority with a predefined margin of –5%. A per-protocol analysis yielded an adjusted treatment difference of –1·3% (–3·6 to 1·1), consistent with the primary analysis. A sensitivity analysis on the ITT population (all 647 randomly assigned participants) with the FDA snapshot algorithm also confirmed the results of the primary analysis, with an adjusted treatment difference of –1·52 (–4·99 to 1·9; figure 2B). The reasons for non-success of treatment are listed (figure 2C).

Ten participants had virological failure, six (2%) of 318 in the intermittent treatment group and four (1%) of 318 in the continuous treatment group, with an adjusted treatment difference of 0·6% (–1·3 to 2·6), and confirmed the non-inferiority of the intermittent strategy for risk of virological failure, with a predefined non-inferiority margin of 4% (figure 2D). Three of the six participants who had virological failure in the intermittent treatment group, and one of the four participants who had virological failure in the continuous treatment group presented new drug-resistance mutations. Specifically, the three participants from the intermittent treatment group displayed M184I, E138K, and Y188L on the reverse transcriptase gene, M184V,

E138K, V179I, and H221Y on the reverse transcriptase gene, M184I drug-resistance mutations on the reverse transcriptase gene, and N155H integrase gene drug-resistance mutations, and the patient from the continuous treatment group presented the K101E/K drug-resistance mutation on the reverse transcriptase gene (table 2).

Subgroup analyses of the proportion of participants with virological failure according to baseline third-agent ART class gave similar findings across all subgroups (figure 2D). Two of the three participants in the intermittent treatment group and one of the three participants in the continuous treatment group who had virological failure while on NNRTI-based therapy developed new resistance mutations. One in three of the participants from the intermittent treatment group and none from the continuous treatment group who had virological failure on an INSTI developed new integrase resistance mutations.

Additional post-hoc subgroup analysis according to demographic or HIV characteristics revealed no significant difference in treatment effects between the various subgroups, except for the lowest CD4 count, for which the intermittent strategy appeared to have a lower risk of virological failure than the continuous strategy (–2·0%, 95% CI –4·8 to 0·8) in participants with a high nadir CD4 value (≥360 cells per µL) and a higher risk (3·1%, 95% CI –0·4 to 6·5) in those with a low nadir CD4 value (<234 cells per µL; $p_{interaction}$=0·023; appendix p 7).

Overall, 31 viral blips occurred in 31 participants; 14 in the intermittent treatment group and 17 in the continuous treatment group, with incidence rates of 5·0 and 6·1 per 100 person-years, respectively, and an estimated incidence rate ratio of 0·82 (95% CI 0·37 to 1·76; appendix p 13).

The changes in CD4 and CD8 T-cell counts, and CD4:CD8 ratio between baseline and week 48 did not differ significantly between the two groups (appendix p 9).

Among the 318 participants treated with the intermittent strategy until week 96, the proportion with therapeutic success at week 96 was 293 (92%, 95% CI 88·6 to 94·8) of 318 participants. From baseline to week 96, therapy was unsuccessful in 25 participants: 14 from baseline to week 48 (including six with virological failure) and 11 from week 48 to week 96 (including seven with virological failure). During the 96 weeks of follow-up, virological failure occurred in 13 (4%, 95% CI 2·2 to 6·9) of 318 participants. Virological failure was observed in eight (5%) of 148 participants (95% CI 2·4 to 10·4) on NNRTIs (six of 118 for rilpivirine, one of 24 for efavirenz, and one of six for etravirine), three (2%) of 152 (95% CI 0·4 to 5·7) on INSTIs (none of 73 for dolutegravir, two of 65 for elvitegravir, and one of 14 for raltegravir), and two (11%) of 18 (95% CI 1·4 to 34·7) on protease inhibitors (two of 16 for darunavir and none of two with atazanavir) at week 96. Overall, among the 13 participants with virological failure, drug-resistance mutations appeared in five participants, one on an NRTI alone, three on an NRTI and NNRTI (on rilpivirine), one on an NRTI and INSTI (on raltegravir).

The frequencies of adverse events are shown in table 3. Overall, from baseline to week 48, 45 grade 3–4 adverse events were reported in 29 participants in the intermittent treatment group and 55 adverse events were reported in 39 participants in the continuous treatment group, with an incidence rate of 15·5 per 100 person-years in the intermittent treatment group and 19·0 per 100 person-years in the continuous treatment group, and an incidence rate ratio of 0·8 (95% CI 0·5 to 1·2). None of the grade 3–4 adverse events were considered by the investigator to be related to the study strategy. During the first 48 weeks of follow-up, two deaths were reported in the intermittent treatment group; one from sudden cardiac arrest, and other from pulmonary adenocarcinoma. No deaths occurred in the continuous treatment group. Two participants discontinued the study treatment because of adverse events; one for grade 1 depression in the intermittent treatment group and one for myocardial infarction in the continuous treatment group.

The change in lipid fractions, glycaemia, AST, and ALT concentrations from baseline to week 48 were also not significantly different between the two treatment groups, except for the change in eGFR, which increased by 3 mL/min (IQR –1 to 9) in the intermittent treatment group versus 0 mL/min (–5 to 5) in the continuous treatment group (p<0·0001 at week 48; appendix p 9). Tolerance between week 48 and week 96 is detailed in the appendix (p 2).

Total HIV DNA concentrations in peripheral blood mononuclear cells was evaluated in the first 120 participants (54 from the intermittent treatment group and 66 from the continuous treatment group). The change in total HIV DNA concentrations in PBMCs from baseline to week 48 did not differ between the two treatment groups (appendix p 10).

Inflammation and immune activation marker concentrations (hsCRP, hsIL-6, IP-10, sCD14, sCD163, sTNFR1, sTNFR2, and d-dimers) were assessed in 46 participants in the intermittent treatment group and 55 participants in the continuous treatment group. The changes in marker concentrations from baseline to week 48 did not differ between the two treatment groups (appendix p 10).

Adherence to the strategy, assessed by questionnaires and tenofovir plasma concentrations, showed a high degree of adherence to the study strategies, as detailed in the appendix (p 2). In the intermittent treatment group, 153 (59%) of 258 participants reported an improvement in daily life satisfaction versus only 19 (7%) of 255 in the continuous treatment group (p<0·0001). Among the eight PROQOL-HIV dimensions, only the change in treatment-impact score from baseline to week 48 differed significantly between the two treatment groups, with the score being 2·9 (SE 0·6) in the intermittent treatment

	Baseline ART regimen	ART regimen at unsuccessful treatment	Time to virological failure	Suspected virological failure or confirmed virological failure (copies/mL)	On or off treatment at the pVL measurement	Adequate plasma drug concentration	Self-reported adherence	DRM* to current treatment in PBMCs at baseline	DRM* to current treatment at unsuccessful treatment	Modification of strategy	Modification of treatment	Virological outcome of pVL <50 copies per mL at most recent visit
Intermittent treatment group												
Participant 1	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Week 12	pVL 83; pVLc 91	Off Off	Yes	Week 12, 4 days, 100 %	No	..	Yes	No	Yes
Participant 2	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Week 12	pVL 713; pVLc 69700	On On	Yes	Week 12, 4 days, 100 %	No	M184I, E138K, and Y188L on the reverse transcriptase gene	Yes	Yes	Yes
Participant 3	Tenofovir alafenamide + emtricitabine + elvitegravir–cobicistat	Tenofovir alafenamide + emtricitabine + elvitegravir–cobicistat	Week 24	pVL 736; pVLc 1710	Off Off	Yes	Week 24, 1 day, 25%	No	..	No	Yes	Yes
Participant 4	Tenofovir alafenamide + emtricitabine + elvitegravir–cobicistat	Tenofovir alafenamide + emtricitabine + elvitegravir–cobicistat	Week 36	pVL 393; pVLc 241	On Off	No	Week 36, 4 days, 100%	No	..	Yes	Yes	Yes
Participant 5	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Week 36	pVL 69; pVLc 129	Off Off	Not done	Week 36, 3 days, 75%	No	M184V, E138K, V179I, and H221Y on the reverse transcriptase gene	Yes	Yes	Yes
Participant 6	Abacavir + lamivudine + raltegravir	Abacavir + lamivudine + raltegravir	Week 48	pVL 331; pVLc 230	Off Off	Yes	Unknown	No	M184I on the reverse transcriptase gene; N155H on the integrase gene	Yes	Yes	Yes
Continuous treatment group												
Participant 7	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Week 36	pVL 60; pVLc 229	On On	Yes	Week 36, 7 days, 100%	No (integrase not amplified)	Reverse transcriptase and integrase not amplified	NA	No	Yes
Participant 8	Abacavir + lamivudine + dolutegravir	Abacavir + lamivudine + dolutegravir	Week 48	pVL 432; pVLc 372	On On	Yes	Week 12, 7 days, 100%; week 48, (unknown)	No (integrase not amplified), but T97A present in 2015 plasma genotype	T97A on the integrase gene	NA	No	Yes
Participant 9	Tenofovir disoproxil fumarate + emtricitabine + efavirenz	Tenofovir disoproxil fumarate + emtricitabine + rilpivirine	Week 48	pVL 1502; pVLc 963	On On	No	Week 48, 4 days, 57%	No	..	NA	Yes	Yes
Participant 10	Abacavir + lamivudine + rilpivirine	Abacavir + lamivudine + rilpivirine	Week 48	pVL 62; pVLc 105	On On	Yes	Week 48, 7 days, 100%	No	K101E/K on the reverse transcriptase gene	NA	Yes	Yes

Intermittent treatment=4 days on and 3 days off. DRM=drug-resistance mutations. pVL=plasma viral load. pVLc=confirmed plasma viral load. NA=not applicable.

Table 2: **Description of participants with virological failure**

	Intermittent treatment group, n=318			Continuous treatment group, n=318				p value
	Participants	Events	Incidence per 100 person-years, 95% CI	Participants	Events	Incidence per 100 person-years, 95% CI	Incidence rate ratio per 100 person-years, 95% CI	
All adverse events	244 (77%)	798	275·1 (256·3–294·8)	242 (76%)	709	244·4 (226·7–263·1)	1·1 (1·0–1·2)	0·022
Grade 3 or 4 adverse events	29 (9%)	45	15·5 (11·3–20·8)	39 (12%)	55	19·0 (14·3–24·8)	0·8 (0·5–1·2)	0·320
Grade 3 or 4 adverse events, occurring in at least 0·5% of participants	NA	NA	NA	NA	NA	NA	NA	NA
Malignant and unspecified neoplasms	7 (2%)	9	NA	4 (1%)	5	NA	NA	NA
Injury, poisoning, and procedural complications	0	0	NA	11 (3%)	12	NA	NA	NA
Cardiac disorders	2 (<1%)	2	NA	3 (<1%)	3	NA	NA	NA
Musculoskeletal and connective tissue disorders	1 (<1%)	1	NA	2 (<1%)	2	NA	NA	NA
Reproductive system and breast disorders	2 (<1%)	4	NA	1 (<1%)	2	NA	NA	NA
Surgical and medical procedures	1 (<1%)	1	NA	6 (2%)	6	NA	NA	NA
Infections and infestations	2 (<1%)	2	NA	3 (<1%)	3	NA	NA	NA
General disorders and administration site conditions	4 (1%)	5	NA	1 (<1%)	1	NA	NA	NA
Nervous system disorders	1 (<1%)	1	NA	3 (<1%)	3	NA	NA	NA
Blood and lymphatic system disorders	3 (<1%)	6	NA	7 (2%)	7	NA	NA	NA
Metabolism and nutrition disorders	2 (<1%)	2	NA	3 (<1%)	3	NA	NA	NA
Investigations	3 (<1%)	6	NA	1 (<1%)	1	NA	NA	NA
Drug-related grade 3 or 4 adverse events	0	0	0 (0–1·3)	0	0	0 (0–1·3)	NA	>0·999
Death	2 (<1%)	2	0·7 (0·1–2·5)	0	0	0 (0–1·3)	NA	0·250
Discontinuation due to adverse events	1 (<1%)	1	0·3 (0–1·9)	1 (<1%)	1	0·3 (0–1·9)	NA	>0·999
Depression	1	1	NA	0	0	NA	NA	NA
Myocardial infarction	0	0	NA	1	1	NA	NA	NA

Data are n (%) and N unless otherwise specified. Incidence was estimated with Poisson regression models. Duration of follow-up was 290·1 person-years in both groups. Intermittent treatment=4 days on and 3 days off. NA=not applicable due to small number of events.

Table 3: **Frequency of adverse events during the first 48 weeks of follow-up**

group versus 0·3 (0·7) in the continuous treatment group (p=0·0039; appendix p 11).

During the 48 weeks of follow-up, the total cost of antiretroviral drugs was €3 604 298; €1 312 542 for the intermittent treatment group and €2 291 756 for the continuous treatment group, corresponding to a 43% decrease in the cost of antiretroviral drug in the intermittent treatment group relative to the continuous treatment group (p<0·0001). The mean annual cost of antiretroviral drugs per participant was estimated at €4127 (SD 888) for the intermittent treatment group and €7207 (1552) for the continuous treatment group.

Discussion

The QUATUOR trial is the first randomised study to date evaluating a 4-days-on and 3-days-off ART maintenance regimen. The intermittent triple-therapy regimen was non-inferior to the standard continuous triple-therapy regimen in maintaining virological suppression over 48 weeks. The difference in treatment success rates between the two groups remained within the predefined 5% non-inferiority margin. The commonly use non-inferiority margin for treatment success is 10%. As the study strategy is an innovative approach, a non-inferiority margin of 5% was chosen to ensure preservation of treatment effect in the intermittent treatment group. Moreover, for virological failure at week 48, the non-inferiority of the intermittent treatment regimen was confirmed with the FDA-defined margin of 4% for switch trials. Analyses of the proportion of participants with virological failure according to the third antiretroviral agent class at baseline showed similar effects across all subgroups.

That participants displaying unsuccessful treatment on NNRTI had emerging disease-resistant mutations might reflect a low genetic barrier to the development of rilpivirine resistance. Interestingly, emerging integrase disease-resistant mutation was observed in only one participant on raltegravir out of the three on an INSTI in the intermittent treatment group at the time of failure, an INSTI for which the genetic barrier to resistance is also low.

The long-term efficacy results at 96 weeks confirms a high therapeutic success rate particularly when using a

high genetic-barrier drug combination. We observed a virological failure for only 2% of participants taking INSTIs (no participants on dolutegravir) and 5% of those taking NNRTIs (5% on rilpivirine).

Viral blips occurred at a similar frequency in the two groups until week 48, as previously reported for two-drug regimens.[16,17] In the virological substudy, ultrasensitive plasma viral load was not found to change significantly over time, and between the two groups,[18] and the amount of proviral DNA, reflecting the reservoir, was stable and similar in the two groups from baseline to week 48, as reported in previous studies of short-cycle ART.[8,14,19] Our data are consistent with an absence of immune degradation and inflammatory activation in individuals on 4-days-on 3-days-off intermittent ART maintenance therapy, as confirmed by the absence of substantial differences in the changes in CD4 T-cell counts, CD4:CD8 ratio, and inflammatory marker concentrations. These findings are reassuring with respect to the report of increased levels of systemic inflammation in people with HIV treated with ART regimens reduced to fewer than three antiretroviral drugs in a retrospective cohort study.[20]

Laboratory parameters remained stable in the two groups. The only improvement observed was a slight improvement in renal creatinine clearance in the intermittent treatment group relative to the continuous treatment group, probably related to the low exposure to tenofovir.

Our strategy is different from older interrupted-treatment strategies, which worked less well and in which the duration of the interruption was longer and drugs with lower genetic barrier to resistance were used.[9–11] The low rate of virological rebound observed here is compatible with the results from treatment discontinuation studies that evoke a latency period of 5–8 days before the resumption of viral replication.[21,22] This latency might be related to the long half-life of NNRTIs or INSTIs.[23–25]

Other switch strategies are now recommended for patients with no history of virological failure, no documented evidence of major drug-resistance mutations, and no hepatitis B virus co-infection. Two-drug regimens based on boosted protease inhibitors associated with lamivudine have been shown to be non-inferior to triple therapy,[26–29] with treatment success rates of 83% to 89·5% at week 48. Two-drug maintenance regimens combining dolutegravir plus rilpivirine or lamivudine[5,30,31] and long-acting cabotegravir–rilpivirine regimens have also been tested in large trials[7,32,33] with a success rate at week 48 ranging from 93% to 95%. However, adverse effects were frequent in these trials following the introduction of new molecules, or because of local reactions after injections of long-acting drugs. Conversely, no new drug was introduced in the QUATUOR trial in which participants were maintained on a stable regimen for at least 4 months before screening. The slightly increased rate of adverse events observed in the intermittent treatment group might be explained by the fact that investigators reported more minor events because of the open-label design. However, we cannot exclude an excess of minor adverse events occurring at reintroduction of the treatment after 3 days of interruption each week.

The QUATUOR study has several limitations that affect the generalisability of the results. First, its open-label design; blinding with the use of a double-dummy design, would not have been feasible, because of the large number of regimens allowed and because the 3-days-off treatment period was at the heart of the strategy. Nevertheless, adherence questionnaires, together with low residual drug concentrations measured during the 3-days-off-treatment period showed a high adherence to the allocated strategy over the follow-up period. We selected a population with a long-term history of previous adherence to treatment that affect the generalisability of the results to a previously adherent patient and we cannot conclude how it would work in less adherent patients. Second, women were unfortunately under-represented in our study. Third, we introduced restrictive virological inclusion criteria in the QUATUOR trial, in which infection with viruses susceptible to all antiretroviral drugs in their ongoing treatment, according to previous plasma RNA or PBMC DNA genotyping, was required. This is not the case in all trials for dual maintenance therapy for example, but it was required by the French authorities for this innovative approach. With our present experience of intermittent therapy, we do not think that PBMC DNA genotyping should be mandatory in patients without virological escape under therapy. Fourth, even though we have shown that the stratified analysis on the third agent is in the three drug classes, it is difficult to extrapolate the efficacy of this strategy to the under-represented third-agent drugs (protease inhibitors, efavirenz, etravirine, or raltegravir). Fifth, the risk of virological failure in the intermittent treatment group compared with the continuous treatment group is high because the CD4 nadir is low. Therefore, the risk-to-benefit assessment of the intermittent strategy should be carefully assessed in patients with low CD4 nadirs. Sixth, our primary evaluation of efficacy and safety at 48 weeks was a short-term evaluation, and one of the hypotheses of our study was that the intermittent strategy would be better tolerated; however, the fact that this was not clearly the case is probably not surprising, given that the participants had been tolerating their current regimen for several years, and were unlikely to develop new longer term toxicities (eg, metabolic and cardiovascular disease) in only 48 weeks of follow-up. However, the long-term safety evaluation at 96 weeks is reassuring.

The 3 day therapeutic weekend was greatly appreciated by the participants, as shown by the high self-reported satisfaction scores for the study regimen. Participants

said that the intermittent strategy was easy to remember and allowed them to live a normal life. Evaluation of satisfaction at week 48 confirmed this finding, with 59% of the intermittent treatment group reporting an improvement in daily life, versus approximately 8% of the continuous group. Furthermore, the PROQOL-HIV questionnaire revealed substantial differences in treatment effect score between the two treatment groups, with a significant improvement in the intermittent treatment group relative to the continuous treatment group. Another advantage of the intermittent strategy is the lower antiviral drug costs, made possible by the high efficiency of this strategy. A saving of about €3080 per patient-year in maintenance therapy was observed. In comparison to dual therapy, this strategy remains less expensive; for example, dual therapy with dolutegravir and lamivudine after a switch from dolutegravir, abacavir, and lamivudine for continuous treatment can save €1735 per patient-year, lower than the intermittent dolutegravir, abacavir, and lamivudine strategy that saves €3764 per patient-year.

In conclusion, the QUATUOR trial showed the non-inferiority of a 4-days-on and 3-days-off ART virological maintenance strategy relative to the standard continuous treatment over 48 weeks, with no effect on cellular reservoir size and no activation of inflammation. Participants in the intermittent treatment group reported higher satisfaction than with their previous continuous strategy, and the incidence of severe adverse events was not higher. A 4-consecutive-days-on and 3-days-off ART maintenance treatment regimen represents a workable, effective, alternative strategy for patients with high adherence to ART, using a high genetic-barrier drug combination.

Contributors

The QUATUOR trial was designed by DC, LA, JL, PDT, PMG, and RL. The trial was coordinated by PDT and RL. BL, CA, CK, JMM, MD, and YY recruited patients and collected data in the trial. DC, JB, KA, and LA were responsible for the acquisition of data. JB and LA wrote the trial analysis plan, did the analysis, verified the data, and had access to the data. LA, PDT, and RL drafted the manuscript. LMJ and SL coordinated and implemented the virological aspects of the study and contributed to manuscript preparation. JCA coordinated and implemented the pharmacological aspects of the study and contributed to manuscript preparation. JC and SF coordinated and implemented the immunological aspects of the study and contributed to manuscript preparation. MD coordinated and implemented the self-reported quality-of-life questionnaire of the study and contributed to manuscript preparation. All authors contributed to interpretation of the data, critically revised the manuscript, and approved the final version.

Declaration of interests

RL has received honoraria from Gilead and ViiV Healthcare and personal grants for attending meetings and travel from ViiV Healthcare, Merck, and Gilead. PDT has received honoraria from Gilead and ViiV Healthcare and personal grants for attending meetings and travel from Gilead, MSD, and ViiV Healthcare. BL has received honoraria for a seminar of medical sales representatives from Gilead. CA has received honoraria for lectures and presentations from ViiV Healthcare, Gilead, Janssen, and MSD and support for attending meeting or travel from Gilead, MSD, and Janssen. CK has received honoraria from MSD and ViiV Healthcare, grants or contracts from ViiV Healthcare and MSD, support for attending meetings and travel from ViiV Healthcare and Gilead and participation on a data safety and monitoring board or advisory board from MSD and ViiV Healthcare. JMM has received grants or contracts for his institution from Gilead, royalties or licenses from Gilead, ViiV Healthcare, and Merck, and a payment for participating on a DSMB or advisory board from Aelix. JC has received research grant for her institution from MSD and ViiV Healthcare, and payment for lectures from Gilead, MSD, and ViiV Healthcare. MD has received grants or contracts from Gilead, ViiV Healthcare, and Abbvie, honoraria from Gilead, ViiV Healthcare, and Merck and support for attending meetings or travel from Janssen and Gilead. LMJ has received honoraria for advisories or invited talks to conferences from Gilead, Merck, MSD, Janssen, and ViiV Healthcare, and support for attending meetings or travel from Gilead, Merck, and MSD. DC has received grant or contracts for HIV grant for her institution from Janssen, and honoraria for two HIV lectures from Gilead. All author authors declare no competing interests.

Data sharing

Individual participant data will be made available (including data dictionaries), and data that underlie the results reported in this Article can be shared after deidentification (text, tables, figures, and appendices) to researchers who provide a methodologically sound proposal, beginning 3 months with no end date following Article publication. Study protocol, statistical analysis plan, and analytical code will also be made available. Proposals should be directed to quatuor@iplesp.upmc.fr; to gain access, data requestors will need to sign a data-access agreement. The data will be sent to the requestor using a security platform.

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References

1 Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. *JAMA* 2016; **316:** 191–210.

2 Katlama C, Ghosn J, Murphy RL. Individualized antiretroviral therapeutic approaches: less can be more. *AIDS* 2017; **31:** 1065–71.

3 Carey D, Puls R, Amin J, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis* 2015; **15:** 793–802.

4 Arribas JR, Girard PM, Paton N, et al. Efficacy of protease inhibitor monotherapy vs triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials. *HIV Med* 2016; **17:** 358–67.

5 Van Wyk J, Ajana F, Bishop F, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose two-drug regimen versus continuing a tenofovir alafenamide-based three or four-drug regimen for maintenance of virologic suppression in adults with HIV-1: phase 3, randomized, non-inferiority TANGO Study. *Clin Infect Dis* 2020; **71:** 1920–29. https://doi.org/10.1093/cid/ciz1243.

6 Soriano V, Fernandez-Montero JV, Benitez-Gutierrez L, et al. Dual antiretroviral therapy for HIV infection. *Expert Opin Drug Saf* 2017; **16:** 923–32.

7 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; **390:** 1499–510.

8 The Breather (PENTA 16) Trial Group. Weekends off breaks in efavirenz based antiretroviral therapy in HIV infected children, adolescents, and young adults (BREATHER): randomised, open label, non-inferiority, phase II/III trial. *Lancet HIV* 2016; **3:** e421–30.

9 Dybul M, Nies-Kraske E, Dewar R, et al. A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection. *J Infect Dis* 2004; **189:** 1974–82.

10 Cohen CJ, Colson AE, Sheble-Hall AG, McLaughlin KA, Morse GD. Pilot study of a novel short-cycle antiretroviral treatment interruption strategy: 48-week results of the five-days-on, two-days-off (FOTO) study. *HIV Clin Trials* 2007; **8:** 19–23.

11 Reynolds SJ, Kityo C, Hallahan CW, et al. A randomized, controlled, trial of short cycle intermittent compared to continuous antiretroviral therapy for the treatment of HIV infection in Uganda. *PLoS One* 2010; **5:** e10307.

12 Bellagamba R, Giancola ML, Tommasi C, et al. Randomized clinical trial on efficacy of fixed-dose efavirenz/tenofovir/emtricitabine on alternate days versus continuous treatment. *AIDS* 2019; **33:** 493–502.

13 Leibowitch J, Mathez D, de Truchis P, et al. Four days a week or less on appropriate anti-HIV drug combinations provided long-term optimal maintenance in 94 patients: the ICCARRE project. *FASEB J* 2015; **29:** 2223–34.

14 de Truchis P, Assoumou L, Landman R, et al. Four-days-a-week antiretroviral maintenance therapy in virologically controlled HIV-1-infected adults: the ANRS 162-4D trial. *J Antimicrob Chemother* 2018; **73:** 738–47.

15 US Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-immunodeficiency-virus-1-infection-developing-antiretroviral-drugs-treatment (accessed Jan 4, 2022).

16 Joly V, Burdet C, Landman R, et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). *J Antimicrob Chemother* 2019; **74:** 739–45.

17 Underwood M, Wang R, Horton J, et al. Dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in the GEMINI studies: viral load rebound including 'blips' through 48 weeks. 10th IAS Conference on HIV Science (IAS 2019); July 21–24, 2019 (abstr MOPEB231).

18 Lambert-Niclot S, Assoumou L, De Truchis P, et al. No significant change on reservoir in QUATUOR: a 4/7 days a week maintenance strategy. CROI 2020; March 8-11, 2020 (abstr 502).

19 Guardo AC, Zarama A, González T, et al. Effects on immune system and viral reservoir of a short-cycle antiretroviral therapy in virologically suppressed HIV-positive patients. *AIDS* 2019; **33:** 965–72.

20 Serrano-Villar S, López-Huertas MR, Gutiérrez F, et al. Reducing ART to less than 3-ARV regimen linked to increased systemic inflammation. 23rd International AIDS Conference 2020; July 6–10, 2020 (abstr OAB0304).

21 Pinkevych M, Cromer D, Tolstrup M, et al. HIV reactivation from latency after treatment interruption occurs on average every 5–8 days: implications for HIV remission. *PLoS Pathog* 2015; **11:** e1005000.

22 Hill AL, Rosenbloom DIS, Siliciano JD, et al. Correction: real-time predictions of reservoir size and rebound time during antiretroviral therapy interruption trials for HIV. *PLoS Pathog* 2016; **12:** e1005778.

23 Jackson A, Moyle G, Watson V, et al. Tenofovir, emtricitabine intracellular and plasma, and efavirenz plasma concentration decay following drug intake cessation: implications for HIV treatment and prevention. *J Acquir Immune Defic Syndr* 2013; **62:** 275–81.

24 Parienti JJ, Das-Douglas M, Massari V, et al. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS One* 2008; **3:** e2783.

25 Parienti JJ, Fournier AL, Cotte L, et al. Forgiveness of dolutegravir-based triple therapy compared with older antiretroviral regimens: a prospective multicenter cohort of adherence patterns and HIV-RNA replication. *Open Forum Infect Dis* 2021; **8:** ofab316.

26 Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15:** 785–92.

27 Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15:** 775–84.

28 Di Giambenedetto S, Fabbiani M, Quiros Roldan E, et al. Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). *J Antimicrob Chemother* 2017; **72:** 1163–71.

29 Pulido F, Ribera E, Lagarde M, et al. Dual therapy with darunavir and ritonavir plus lamivudine versus triple therapy with darunavir and ritonavir plus tenofovir disoproxil fumarate and emtricitabine or abacavir and lamivudine for maintenance of HIV-1 viral suppression: randomised, open label, non-inferiority DUAL-GESIDA 8014-RIS-EST45 trial. *Clin Infect Dis* 2017; **65:** 2112–18.

30 Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018; **391:** 839–49.

31 Rial-Crestelo D, de Miguel R, Montejano R et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: week 96 results of ART-PRO pilot study. *J Antimicrob Chemother* 2020; **17:** dkaa479.

32 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.

33 Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med* 2020; **382:** 1112–23.