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# Is intermittent antiretroviral therapy a satisfactory strategy for the management of patients living with HIV?

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## Abstract

***Many innovations, such as long-acting agents, new delivery modalities (injectable and nanoparticles), and novel paradigms (immunotherapy or dual therapy), have been introduced to facilitate the administration of antiretroviral treatment (ART) to patients infected with HIV and improve their adherence and quality of life without altering the drugs' effectiveness. Studies have investigated the use of intermittent treatment, especially weekends-off ART in HIV-suppressed patients. In this review, we analyzed data concerning intermittent ART to help determine if this strategy is reasonable for the management of patients living with HIV. The results of early studies, in 2007-2015, were encouraging, but the studies were flawed because of the small number of patients included, the absence of a control arm, and random designs with variable patterns of ART administration. From 2016, studies have included more patients, and some are prospective, randomized controlled studies. While non-nucleoside reverse transcriptase inhibitors have been most studied, treatment with integrase inhibitors also has been reported, with the findings that viral resistance did not appear when treatment failed with dolutegravir but not with raltegravir. The most recent study, QUATUOR, found that a 4-day on, 3-day off pattern was non-inferior to the continuous pattern (7 days on). Better-quality studies with long-term follow-up (96 weeks or more) are needed to determine the validity of intermittent treatment and the optimal regimens and monitoring to be used in the management of virologically suppressed patients living with HIV. (AIDS Rev. 2021;23:117-125)***

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## Keywords

***HIV. Antiretroviral treatment. Short-cycle treatment. Intermittent antiretroviral therapy. Persons living with HIV.***

## Introduction

The introduction of antiretroviral therapy (ART) has led to a 56% decrease in AIDS-related deaths since the peak in 2004[1]. Life expectancy of people living with HIV (PLWHIV) has increased to nearly that of the general population[2]. With longer life expectancy, PLWHIV need more than control of viral replication;

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they need a better quality of life. Innovative developments in ART, including long-acting agents, new delivery modalities (injectable, nanoparticles), and novel paradigms, such as immunotherapy, dual therapy, or intermittent ART should be exploited to provide a better life for PLWHIV[3]. European and American guidelines[4,5] recommend tritherapy as first-line treatment, preferably including integrase inhibitors (INI) (dolutegravir or bictegravir) in combination with two nucleoside reverse transcriptase inhibitors (NRTI) (emtricitabine or lamivudine) plus tenofovir disoproxil or tenofovir alafenamide. The World Health Organization has also suggested treatment with efavirenz and NRTI backbone as an alternative[6]. Dual therapy with dolutegravir and lamivudine has been found non-inferior to tritherapy with tenofovir alafenamide or tenofovir disoproxil in naïve HIV-infected patients or as ART simplification in well-suppressed patients[7]. These studies have led the European AIDS Clinical Society, the Department of Health and Human Services, and the International AIDS Society to recommend dual therapy combining dolutegravir and lamivudine as the preferred first-line treatment in patients without hepatitis B co-infection, no demonstrated resistance, and a viral load less than 500,000 copies/mL, or as treatment simplification in patients with well-controlled disease[8,9]. In patients with CD4 < 200/mm$^3$, the International AIDS Society guidelines still caution about the use of dolutegravir and lamivudine as initial treatment[9].

Furthermore, with the aim of simplifying treatments to facilitate patient compliance and reduce exposure to ART (reduce toxicity) and provide a better quality of life, several groups[10-22] have evaluated the use of intermittent treatment (especially, weekends off ART). Patients report that this practice is common among them, especially among adolescents[23] or in adults with poor adherence. In this review, we analyzed past and current data concerning intermittent ART, especially weekends off, to see whether this strategy is reasonable for the management of some PLWHIV.

## *Pilot studies*

The first studies of intermittent ART were conducted between 2007 and 2015 (Table 1). Those studies were flawed because of the small number of patients included, the absence of a control arm, or highly variable ART patterns. The first study on the subject, FOTO[11], found the rate of undetectable viral load at least 78% at 48 weeks in 30 PLWHIV during a transition to intermittent treatment (5 days on, 2 days off, for at least 3 months). Of these 30 patients, ten received efavirenz-based treatment, ten received a boosted protease inhibitor (PI)-based treatment, and ten received nevirapine-based treatment. HIV viral load was undetectable at 48 weeks in 100% of patients treated with efavirenz, 78% treated with PI, and 89% treated with nevirapine. However, because of few patients and the absence of control arms, conclusions could not be drawn. In 2010, Reynolds et al.[12] conducted a randomized controlled study of 146 patients who had undetectable viral loads, 98% of whom were receiving efavirenz-based treatment. The study had three arms: continuous treatment; intermittent treatment of 7 days on, 7 days off; and a short-cycle treatment of 5 days on, 2 days off. The 7-day on, 7-day off arm was discontinued because of a 31% virological failure rate at mid-study. At 72 weeks, the virological failure rate was 11.5% in the short-cycle treatment arm and 21.6% in the continuous-treatment arm. Leibowitch et al.[13,14] conducted two studies: the first[13], in 2010, comprised eight patients, and the second, ICCARE[14], in 2015, comprised 94 patients; the studies were of prospective, not comparative, and design. The selection criteria were poorly defined, and the type of ART was variable. The patients, selected on a voluntary basis, took their treatment according to a cycle of 5 days on and 2 days off, then 4 days on and 3 days off. On this short-cycle therapy, no virological failure was seen at 84 weeks[13] and 87 weeks[14]. Later, an increasingly small proportion of patients dropped the on-treatment weekdays on, from 3 days to 1 day. The rates of virological failure were variable but encouraging (Table 1), although conclusions cannot be drawn because of the few patients included the lack of a control arm, and the poorly defined duration of treatment. Furthermore, although the ICCARE study[14] had an 84% virological failure rate in patients taking raltegravir-based ART on a 3-day on, 4-day off regimen, the drug was administered at a dose of 400 mg once a day, whereas the full dose of raltegravir is 400 mg twice a day or 1200 mg once a day[4-6].

Others[15,16] have hypothesized that structured-treatment interruption can enhance immune responses (in acute or chronic HIV infection) and decrease the drug exposure and toxicity. However, the short-treatment interruption strategy has not been proven safe in the short and long term[17]; furthermore, the development of resistance with this approach has been reported[17,18].

**Table 1. Pilot studies of intermittent antiretroviral treatment**

| Study | Authors | Year | Study design | Total patients included (test/control) | Inclusion criteria | Exclusion criteria | CD4+ count | Cycle on/off | ART group test N (%) | VL undetect. duration (years) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| FOTO[11] | Calvin J. Cohen, Amy E. Colson, Alexander G. Sheble-Hall, et al. | 2007 | Open-label, single-arm, prospective pilot study | 30 | HIV 1 infection<br>CD4 + > 200/mm<br>≥ VL undetectable for ≥ 3 months<br>Treatment with stable ART combination<br>PI-treated patients with virological failure on prior PI-based regimen admitted | NNRTI-based regimen with previous virological failure on prior NNRTI-based regimen | 612 | 5/2 | Efavirenz-based (10)<br>PI-based (10)<br>Nevirapine-based (10)<br>70% : Not first line ART | ≥ 3 months | 48 weeks :<br>Undetectable rate;<br>Efavirenz: 100%<br>Nevirapine: 89%<br>PI: 78% |
| Reynolds et al. 2010[12] | Steven J. Reynolds, Cissy Kityo, Claire W. Hallahan, et al. | 2010 | RCT, non-inferiority | 146 (32 (7/7)/ 57 (5/2)/ 57) | – CD4+ ≥ 125 c/mm ≥<br>– VL <50 c/mL | | 264 | 7/7<br>5/2 | ART including<br>Boosted PI based ART (1.8%)<br>or<br>Efavirenz-based ART (98%)<br>If nevirapine; switch to PI or Efavirenz | 48 sem (ART exposition) | **72 weeks**<br>ART failure (VL ≥ 10.000 c/mL or > 1.000 c/mL on 2 measurements or > 400c/mL at the end of the study)<br>**7/7 arm: 31% >> Stopped**<br>5/2 arm: 11.5%<br>Continuous arm: 21.6%<br>CD4 + count (decrease > 30%)<br>5/2: 1<br>not statistically different<br>Adverse events (AE):<br>Reduction of lipodystrophy and lactic acidoses |

*(Continues)*

**Table 1. Pilot studies of intermittent antiretroviral treatment *(Continued)***

| Study | Authors | Year | Study design | Total patients included (test/control) | Inclusion criteria | Exclusion criteria | CD4+ count | Cycle on/off | ART group test N (%) | VL undetect. duration (years) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Leibowitch et al. 2010[13] | Jacques Leibowitch, Dominique Mathez, Pierre de Truchis, et al. | 2010 | Single arm, prospective | 48 (39) (12) | Selection on the basis on the volunteering's patient and adherence to repeated monitoring | | 154 ± 82 | 5/2 et 4/3 (3/4) (2/5) | Backbone NRTI:<br>91% emtricitabine+tenofovir disoproxil + 32.4% Efavirenz<br>35.6% Boosted PI<br>1.3% INI<br>Triple NRTI backbone (Didanosine +lamivudine+tenofovir disoproxil) +<br>NNRTI: 20.4%<br>NNRTI: 56.5%<br>Boosted PI: 40.4% | 5.5 ± 2.8 (ART exposition) | Virological failure (VL > 50c/mL):<br>5/2: 0/48 (56w)<br>4/3: 0/47 (84w)<br>3/4: 4/39 (50w)<br>2/5: 2/12 (24w) |
| ICCARE[14] | Jacques Leibowitch, Dominique Mathez, Pierre de Truchis, et al. | 2015 | Single-arm, prospective | 94 (84) (66) (12) | – Written informed consent<br>– Tri ou quadritherapy 7 days/7<br>– VL < 50 c/mL for ≥ 5 months | | 181 ± 98 | 4/3 (3/4) (2/5) (1/6) | 2 NRTI (emtricitabine, tenofovir, abacavir, or didanosiene)<br>+<br>[Boosted PI<br>(Lopinavir, atazanavir, darunavir or amprenavir)<br>or<br>NNRTI<br>(Evafirenz, nevirapine, or etravirine)]<br>OR<br>Combinaisons 3 NRTI+NNRTI<br>OR<br>Others combinations :<br>i. Raltegravir + etravirine+boosted PI<br>ii. 2-3 NRTI + etravirine<br>iii. LPV/r + didanosine | 6.3±4 (ART exposition) | 87 weeks; virological failure rate:<br>4/3: 0%<br>3/4: 11.9%<br>2/5 10.6%<br>1/6: 8.3%<br>Raltegravir-based treatment given 3 days/4:<br>87% virological failure |

## Recent studies

Studies conducted from 2016 (Table 2) include more patients than in earlier studies, and most studies were randomized and controlled. In 2016, the BREATHER study[19] included 199 HIV-infected patients who had undetectable HIV for at least 12 months on efavirenz-based ART. The 99 patients in the test arms adopted a 5-days-on, 2-days-off pattern. At 48 weeks, there was no significant difference in rates of virological failure or acquisition of resistance between the two groups. The extended follow-up BREATHER study[20] took over the same patients for follow-up to 96 and 144 weeks; there was no significant difference in outcome between continuous intake and the 5-day-on and 2-day-off treatment patterns. The 2017 ANRS 162-4D[21] study was a single-arm, prospective study of HIV-infected patients whose disease had been well-controlled for 12 months on ART consisting of 2 NRTI plus a boosted PI (mainly 15% darunavir/ritonavir or a non-nucleoside reverse transcriptor inhibitors) (NNRTI) (mainly 40% efavirenz). After 48 weeks of a 4-day on, 3-dayoff regimen, HIV was undetectable in 96% of patients. Viral blips (n = 4) were more frequent with rilpivirine, atazanavir, and lopinavir-based regimens. The most recent randomized and controlled non-inferiority study, QUATUOR[22], include a large number of patients (n = 636), with 318 in each arm (4-days on, 3-days off arm [4D/7] vs. 7-days-on arm [7D/7]). The selected patients were required to have an undetectable viral load for at least 12 months, no resistance in their genotype, and ART consisting of two associated NRTI (tenofovir disoproxil or tenofovir alafenamide base [72.3%]) with a boosted PI (5.2%) or NNRTI (46.5% in which 80% was efavirenz) or INI 47.8% mainly dolutegravir or elvitegravir. The primary end point was the proportion of patients with therapeutic success at week 48, defined by no virological failure (confirmed viral load > 50 c/mL) and no interruption of treatment (except for pregnancy or change of molecular form of drug in the same class). Secondary end points were virological failure at week 48, drug resistance, safety, tolerability, and drug plasma concentration at time of virological failure. After 48 weeks, therapeutic success was 95.6% in the 4D/7 arm and 97.2% in the 7D/7 arm. There was no statistically significant difference between the two groups in rate of virological failure (1.9% in the 4D/7 arm vs. 1.3% in the 7D/7 arm) or adverse effects. Virological failure in the INI-based regimen was 0.7% in the 7D/7 arm and 2.0% in the 4D/7 arm. In the NNRTI-based regimen, the virological failure rate was 2.1% in the 7D/7 arm and 2.0% in the 4D/7 arm. No patient failed in the PI-based regimen. When patients failed with INI, resistance was seen with raltegravir but not with dolutegravir, and when they failed with NNRTI, resistance appeared with rilpivirine (Table 2). There was no difference between the two arms in the frequency of viral blips or adverse events during treatment. We are awaiting the 96-week results.

## Discussion

With the introduction of ART, remarkable progress has been made in the experience of PLWHIV, especially in their rates of morbidity and mortality. However, these favorable outcomes require the continuous intake of an ART with strict compliance. The main hypothesis explaining this necessity is the existence of reservoirs: specific cell types and anatomical sites where the virus persists despite absence of blood viremia[23-25]. Reservoirs are established during the primary HIV infection[25], hence the importance of introducing treatment as early as possible. Viral blips can be explained by transiently increased viral replication within these sanctuaries or by a decrease in the patient's compliance with ART. Adherence to treatment is critical in the management of PLWHIV, which is especially challenging for certain groups: those who doubt the diagnosis, those who want to hide it, and adolescents, whose fear of stigma, personal questioning, and the desire for autonomy may interfere with their treatment[26]. Intermittent treatment, such as weekend-free treatment, is an approach that is less restrictive and may increase patient compliance[19,20].

The results of the first studies on intermittent treatment of HIV disease were encouraging, but the studies were flawed because of the small number of patients included, the absence of a control arm, or a random design with highly variable ART patterns. Recent studies, though, have yielded more persuasive evidence that intermittent ART is safe and without virological failure. Indeed, most new studies have found non-inferiority of a discontinuous pattern (up to a maximum of 4 days on and 3 days off) in comparison with continuous treatment. The latest randomized controlled study, QUATUOR[22], which included a large sample of patients, confirmed the results of other studies and reinforced the clinical impression that patients often independently discontinue their treatment. However, studies with longer-term follow-up, or extension of recent studies, to 96 weeks are needed to verify these

**Table 2. Recent studies of intermittent antiretroviral treatments.**

| Study | Authors | Year | Study design | N total patients included (test/ control) | Inclusion criteria's | Exclusion criteria's | CD4 + count | Cycle on/off | ART group test n (%) | VL undetect. duration (years) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BREATHER (PENTA16)[19] | Karina Butler, Jamie Inshaw, Deborah Ford, et al | 2016 | Randomized, controlled, non-inferiority trial | 199 (99/100) | – HIV 1 infected peoples<br>– 8–24 years<br>– CD4 ≥ 350 cells/mm ≥<br>– VL < 50 c/mL for ≥ 12 months<br>– Efavirenz based ART<br>– VL blips > 50 and < 1000 c/mL can be enrolled<br>– Assay that detect RNA VL ≥ 50 c/mL<br>– 1st line ART regimen<br>– Efavirenz based TAR+2 NRTI for 12 months | – Pregnancy (or risk)<br>– Acute illness<br>– Concomitant therapy for an acute illness<br>– Creatinine or liver enzymes elevation (Grade 3 or above)<br>– Nevirapine or boosted PI regimen<br>– Previous ART monotherapy (except for prevention of mother–to–child transmission) | 793 | 5/2 | Efavirenz – based ART + Zidovudine/ lamivudine 52 (53)<br>or<br>Tenofovir, lamivudine/ emtricitabine 25 (25)<br>or<br>Abacavir, lamivudine/ emtricitabine 22 (22) | 12 months min. | 48 weeks:<br>No significative difference about:<br>– Virological failure (VL > 50 cop/mL); 1.2%<br>– Resistance acquisition<br>– CD4 count<br>– AE |
| BREATHER extended follow–up[20] | Anna Turkova, Cecilia L. Moore, Karina Butler, et al | 2017 | Randomized, controlled, non-inferiority trial | BREATHER 199 (99/100) | – HIV 1 infected peoples<br>– 8–24 years<br>– CD4 ≥ 350 cells/mm ≥<br>– VL < 50 c/mL for ≥ 12 months<br>– Efavirenz based ART | – Pregnancy (or risk)<br>– Acute illness<br>– Concomitant therapy for an acute illness<br>– Creatinine or liver enzymes elevation (Grade 3 or above) | 350–500 14%<br>> 500 86% | 5/2 | | 12 months min<br>6.1 (ART exposition) | 96 et 144 weeks:<br>No significative difference about:<br>– Virological failure; 2%<br>– AE<br>– CD4+count<br>– Mutations |
| ANRS 162–4D trial[21] | Pierre de Truchis, Lambert Assoumo, Roland Landman, et al. | 2017 | Single-arm, prospective multicenter trial | 100 | – HIV 1 infected peoples<br>– ≥ 18 ans<br>– ART for ≥ 12 months<br>– VL ≤ 50 c/mL for ≥ 12 months<br>– No genotype resistance<br>– CD4+ > 250 for ≥ 6 months<br>– ART: 2 NRTI + PI boosté (darunavir, lopinavir, and atazanavir) ou NNRTI (efavirenz, rilpivirine, etravirine) | | 665 | 4/3 | Efavirenz: 40 (40)<br>Rilpivirine: 26 (26)<br>Etravirine: 5 (5)<br>Darunavir/ritonavir: 15 (15)<br>Atazanavir/ritonavir: 13 (13)<br>Lopinavir/ritonavir: 1 (1) | 4<br>5.1 (ART exposition) | 48 weeks:<br>96% VL < 50 copies/mL<br>4 viral blips:<br>Rilpivirine (2)<br>Atazanavir/ ritonavir<br>Lopinavir/ ritonavir |

(Continues)

**Table 2. Recent studies of intermittent antiretroviral treatments *(Continued)***

| Study | Authors | Year | Study design | N total patients included (test/ control) | Inclusion criteria's | Exclusion criteria's | CD4 + count | Cycle on/off | ART group test n (%) | VL undetect. duration (years) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ANRS 162–4D trial[21] | | | | | – No change in ART regimen in the previous 4 months<br>– laboratory tests: GFR > 60mL/min, AST-ALT 3x ULN (upper limit of normal), Hb > 10g/dL, platelets> 100.000/$mm^3$<br>– Pregnancy test negative, contraception during the study<br>– Written informed consent | | | | | | |
| QUATUOR[22] | R. Landman, P. De Truchis, L. Assoumou, et al (ANRS - France) | 2019 | Randomized, open-label controlled, multicenter, non-inferiority trial | 636 (318/318) | – VL < 50 copies/mL for ≥ 12 months<br>– No genotype resistance<br>– CD4 > 250 cells/$mm^3$<br>– PI-, NNRTI- ou INI- based regimen with a 2 NRTI backbone | – No complete genotype or resistance<br>– No virological criteria | 689 | 4/3 | Tenofovir disoproxil or tenefovir alafenamide/ emtricitabine 230 (72.3)<br>abacavir/lamivudine 88 (27.7)<br>INI (dolutegravir/ elvitegravir/ raltegravir) 152 (47.8) (73/65/14)<br>NNRTI (rilpivirine/ efavirenz/etravirine) 148 (46.5) (118/24/6)<br>PI (darunavir/ atazanavir/lopinavir) 18 (5.7) (16/2/0) | 5.1 | 48 weeks: No significative difference about:<br>– Virological failure: 0.6%<br>– Adverse events (AE)<br>– Deaths |

results. In studies with regimens of less than 4 days on, the results are in doubt because of random designs, too few patients included, or the use of raltegravir, where a rate of virological failure of 84% was observed in 2010[13].

The explanation for variation in therapeutic responses is most likely pharmacological. Despite the weak genetic barrier of NNRTIs, which are the most used in studies, their half-life is the longest (efavirenz, 40-55 h or rilpivirine, 45-50 h), whereas the half-life of PI is shorter (darunavir/ritonavir, 15 h; atazanavir/ritonavir, 9-12 h; and lopinavir, 4-6 h), like that of INI (raltegravir, 9 h; elvitegravir/cobicistat, 13 h; and dolutegravir, 14 h)[26]. However, the low rate of virological failure with intermittent intake (4 days on, 3 days off) of boosted PI is partially explained by their long intracellular half-life and high binding affinity, especially for darunavir, which has a dissociative half-life of > 240 h[21,27]. Nevertheless, the more recent QUATUOR study[22], which was randomized and controlled, showed virological control also for the intermittent intake of INI (ART of 47.8% of participants in the study, mainly with dolutegravir and elvitegravir).

Intermittent ART intake results in less long-term exposure to ART and less potential long-term toxicity for the same efficacy[12], especially when treatment is started at a young age.

The economic analysis of the BREATHER study revealed that short-cycle treatment allows a better quality of life and a clear patient preference for this type of regimen. In addition, for equivalent efficiency, this regimen markedly reduces the cost because of less ART consumption. This pattern is therefore considered "cost effective," although more frequent patient visits and tests may offset the cost advantages[28].

Although short-cycle treatment seems non-inferior to continuous treatment, several issues and questions remain unresolved: why do the current guidelines[4-6,8] not recommend short-cycle treatment? One response may be that because of the long half-life of the drugs, short-cycle treatment does not reduce drug exposure and adverse effects. Second, during treatment failures, resistance to the agents used was not evident; therefore, should we favor continuous treatment or change the therapeutic class? Finally, it would be useful to specify how patients who are receiving short-cycle treatment should be monitored; should the virological testing be carried out according to classic protocols or more frequently, and should the classical viral load test or the ultrasensitive assay be used ? Is monitoring of plasma levels even useful, considering that in QUATUOR[22], plasma drug levels were adequate despite virological failure.

Data on a prolonged follow-up with short-cycle treatment, at least 96 weeks, would be relevant. Furthermore, as short-cycle treatment has been demonstrated to be non-inferior, it would be useful to have comparative data on results with the various molecules used in this treatment strategy to help in choosing the optimal regimen. All the studies available have been carried out for simplified treatment of patients with good virological control; data are not available for the initiation of treatment in patient's naïve to any antiretroviral treatment. We have yet to define the ideal regimen, the best candidates for these intermittent regimens, and what clinical and virological monitoring will be necessary.

## Conclusions

Intermittent antiretroviral therapy for patients living with HIV may be safe, without virological failure, and non-inferior to continuous treatment. However, data on the use of intermittent treatment in this population are inconclusive. Better-quality studies with long-term follow-up (96 weeks or more) are needed to determine the validity of intermittent treatment and the optimal regimens and agents to be used.

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