Clinical Infectious Diseases

MAJOR ARTICLE

Dolutegravir Monotherapy Versus Dolutegravir/Abacavir/Lamivudine for Virologically Suppressed People Living With Chronic Human Immunodeficiency Virus Infection: The Randomized Noninferiority MONotherapy of TiviCAY Trial

Laurent Hocqueloux,[1] François Raffi,[2] Thierry Prazuck,[1] Louis Bernard,[3] Simon Sunder,[4] Jean-Luc Esnault,[5] David Rey,[6] Gwenaël Le Moal,[7] Mariam Roncato-Saberan,[8] Marie André,[9] Eric Billaud,[2] Antoine Valéry,[10] Véronique Avettand-Fènoël,[11] Jean-Jacques Parienti,[12,a] and Clotilde Allavena,[2,a]; for the MONCAY study group*

[1]Service des Maladies Infectieuses et Tropicales, CHR d'Orléans–La Source, [2]Service des Maladies Infectieuses, CHU Hôtel Dieu and INSERM UIC 1413 Nantes University, [3]Service des Maladies Infectieuses, CHU Bretonneau, Tours, [4]Service des Maladies Infectieuses et Tropicales, CHG de Niort, [5]Service des Maladies Infectieuses, CHD de Vendée, La Roche-sur-Yon, [6]Le Trait d'Union, Hôpitaux Universitaires de Strasbourg, [7]Service des Maladies Infectieuses, CHU La Milétrie, Poitiers, [8]Service des Maladies Infectieuses, Groupe Hospitalier de La Rochelle–Ré–Aunis, [9]Service des Maladies Infectieuses, CHRU-Brabois, Nancy, [10]Département d'Informatique Médicale, CHR d'Orléans–La Source, [11]Laboratoire de Microbiologie clinique, CHU Necker and Université Paris Descartes, Sorbonne Paris Cité, and [12]Unité de Biostatistique et de Recherche Clinique, CHU de Caen; EA2656 Groupe de Recherche sur l'Adaptation Microbienne (GRAM 2.0), Université Caen Normandie, Caen, France

(See the Major article by Braun et al on pages 1489–97 and Editorial Commentary by Rijnders and Rokx on pages 1506–8.)

Background. We investigated whether dolutegravir (DTG) monotherapy could be used to maintain virological suppression in people living with human immunodeficiency virus (HIV) on a successful dolutegravir-based triple therapy.

Methods. MONCAY (MONotherapy of TiviCAY) was a 48-week, multicentric, randomized, open-label, 12% noninferiority margin trial. Patients with CD4 nadir >100/µL, plasma HIV-1 RNA <50 copies/mL for ≥12 months, and stable regimen with DTG/abacavir (ABC)/lamivudine (3TC) were 1:1 randomized to continue their regimen or to DTG monotherapy. The primary endpoint was the proportion of patients with HIV RNA <50 copies/mL at week 24 in intention-to-treat snapshot analysis. Virologic failure (VF) was defined as 2 consecutive HIV RNA >50 copies/mL within 2 weeks apart.

Results. Seventy-eight patients were assigned to DTG monotherapy and 80 to continue DTG/ABC/3TC. By week 24, 2 patients in the DTG group experienced VF without resistance to the integrase strand transfer inhibitor (INSTI) class; 1 patient discontinued DTG/ABC/3TC due to an adverse event. The success rate at week 24 was 73/78 (93.6%) in the DTG arm and 77/80 (96.3%) in the DTG/ABC/3TC arm (difference, 2.7%; 95% confidence interval [CI], −5.0 to 10.8). During subsequent follow-up, 5 additional VFs occurred in the DTG arm (2 of which harbored emerging resistance mutation to INSTI). The cumulative incidence of VF at week 48 was 9.7% (95% CI, 2.8 to 16.6) in the DTG arm compared with 0% in the DTG/ABC/3TC arm ($P = .005$ by the log-rank test). The Data Safety Monitoring Board recommended to reintensify the DTG arm with standardized triple therapy.

Conclusions. Because the risk of VF with resistance increases over time, we recommend avoiding DTG monotherapy as a maintenance strategy among people living with chronic HIV infection.

Clinical Trials Registration. NCT02596334 and EudraCT 2015-002853-36.

Keywords. dolutegravir; maintenance; monotherapy; virologic failure; INSTI resistance.

Antiretroviral therapy as soon as possible and for life is now universally indicated in human immunodeficiency virus (HIV) infection [1–3]. Although benefits of triple therapy are not debated, reducing the number of drugs (ie, fewer than 3 or even 4, if a booster is used) may be helpful for people living with HIV (PLHIV) to endure lifelong drug exposure and daily burden and to prevent long-term toxicities. This is particularly suitable for aging PLHIV with comorbidities and subsequent comedications who are at a higher risk of drug–drug interactions and drug-related toxicities. Finally, it could reduce costs.

Importantly, recent studies have proven that some dual regimens, based on a boosted protease inhibitor (bPI) or dolutegravir (DTG), a second-generation integrase strand transfer inhibitor (INSTI), are virologically noninferior to triple therapy both in maintenance and first-line strategies [4–8]. By contrast,

Received 1 October 2018; editorial decision 25 November 2018; accepted 29 December 2018; published online January 2, 2019.

[a]J. J. P. and C. A. contributed equally to this work.

*List of all contributors (MONCAY [MONotherapy of TiviCAY] study group) in the Notes section.

Correspondence: L. Hocqueloux, Service des Maladies Infectieuses, CHR d'Orléans – La Source, Orléans, France (laurent.hocqueloux@chr-orleans.fr).

Clinical Infectious Diseases® 2019;69(9):1498–505

DOI: 10.1093/cid/ciy1132

monotherapy, which has been fully investigated with bPI, has failed to prove noninferiority over prolonged follow-up [9].

DTG is a powerful INSTI with a high genetic barrier, overall good tolerance, easy schedule, and few drug–drug interactions [10]. It has also demonstrated superiority to darunavir, a bPI with high potency and genetic barrier to resistance [11]. Taking into consideration its profile, DTG looked to be the ideal candidate for maintenance monotherapy at the end of 2015. In a proof-of-concept study of 21 virologically controlled patients, we reported 100% virologic suppression with DTG monotherapy after a median of 32 weeks [12].

Based on these observations, we conducted the MONCAY (MONotherapy of TiviCAY) trial to determine whether a switch to DTG monotherapy would be noninferior to continuation of a DTG-based standardized triple therapy in maintaining virological suppression.

METHODS

Study Design and Patients

MONCAY was a registered, academic, 48-week, randomized, open-label, noninferiority trial conducted in 9 French HIV reference centers. Main inclusion criteria were chronically HIV-1–infected adults (aged ≥18 years); CD4 nadir >100/μL; no previous AIDS-defining event (excluding a healed tuberculosis); current well-tolerated triple therapy combining DTG, abacavir (ABC), and vudine (3TC) for at least 1 month; and plasma HIV-1 RNA <50 copies/mL for more than 12 months and below the threshold of the method used by the local laboratory (ie, <20 or <40 copies/mL) at the screening visit. Main exclusion criteria were history of documented virologic failure (VF) on INSTI-based regimen, history of genotypic resistance to any INSTI, women of childbearing potential without contraception, creatinine clearance <50 mL/min, chronic hepatitis B virus infection, and any grade 3–4 laboratory abnormality at screening visit. Participants were advised to avoid any unprotected sex.

Ethics

The Tours-Centre-Ouest-1 Ethics Committee approved the MONCAY trial. All participants provided written informed consent. The study was conducted in accordance to the Good Clinical Practice and ethical principles of the Declaration of Helsinki.

Randomization and Masking

Eligible participants were randomly assigned (1:1) to either continue DTG/ABC/3TC (as a single tablet regimen) or to switch to DTG monotherapy (50-mg pill once daily) for 48 weeks. Randomization was made via a website by computer-generated permuted blocks of 4 with stratification by center.

Study Procedures

Study visits were scheduled at screening, baseline, and weeks 4, 12, 24, 36, and 48. Medical history (including all available HIV RNA and DNA genotypes using Sanger sequencing) was collected at the screening visit. Blood samples were drawn for analyses at each site, including blood cell counts (including T-cell counts), HIV RNA, and serum chemistry to assess renal and hepatic parameters. Estimated glomerular filtration rate (eGFR) was calculated with the MDRD equation. Fasting (overnight or >6 hours) serum lipids were measured at baseline and weeks 24 and 48. Self-reported adherence questionnaires were completed by participants at week 4, 24, and 48 visits.

HIV RNA was measured at local laboratories of each site with available viral load assays with no change in the kits throughout the trial. VF was defined as 2 consecutive HIV RNA >50 copies/mL separated by at least 14 days. In case of confirmed VF, resistance testing was performed using genotype sequencing on reverse transcriptase and integrase using the Agence Nationale de Recherche sur le Sida AC11 algorithm [13]. The 3'PPT region was also amplified and compared with HXB2 sequence. An independent data safety monitoring board (DSMB) reviewed all confirmed VF in a real-time manner with a preplanned interim analysis after the first 2 VFs and a stopping rule in case of more than 5 VFs in the experimental arm.

Endpoints

The primary endpoint was the proportion of patients with HIV RNA <50 copies/mL at week 24, as determined with the use of the snapshot algorithm from the US Food and Drug Administration (FDA).

Secondary endpoints included the incidence of emergent genotypic resistance to the INSTI class, virological success at week 48, safety and tolerance, and changes from baseline to week 48 in CD4 cell count, CD4:CD8 ratio, eGFR, lipids (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides) in both arms.

Statistical Analyses

The sample size was computed to demonstrate the noninferiority of the DTG arm compared with the DTG/ABC/3TC arm, with a noninferiority margin of 12%, the most commonly used margin in this setting at the time this study was designed [4, 5, 14]. Assuming a 95% response rate in the DTG/ABC/3TC arm, we calculated that 70 evaluable participants were required in each arm to have a 90% power to determine noninferiority of the experimental arm at a 1-sided significance level of 2.5%.

Noninferiority of the DTG arm could be concluded if the upper bound of a 2-sided 95% confidence interval (CI) for the Newcombe hybrid score risk difference in the primary endpoint (DTG/ABC/3TC minus DTG) was less than 12%.

The primary analysis was by intention-to-treat (ITT; missing or switch equals failure) at week 24, using the FDA snapshot algorithm. Sensitivity analyses examined the primary endpoint by modified ITT (mITT, excluding patients who had exclusion criteria or withdrew consent) and per-protocol (PP, excluding

mITT patients with major protocol deviation) populations. All datasets should be consistent to claim noninferiority, according to the CONSORT statement [15, 16]. Safety analyses were performed in the ITT population. During extended follow-up, the incidence of VFs in both treatment arms was compared using Kaplan-Meier curve and log-rank test. Secondary endpoints were compared between arms using nonparametric Wilcoxon or Mann-Whitney tests, Fisher exact test, or χ^2 test according to the data. All analyses were conducted with SAS V9.4 (SAS Institute, Cary, NC).

When the first negative signal on DTG monotherapy was presented at an international conference (mid-February 2017) [14, 17], the MONCAY study had already enrolled 90% of participants. The steering committee and the sponsor decided to continue the current study because of methodological limitations of other studies and because the protocol-stopping rule had not been fulfilled.

RESULTS

Participants

Between January 2016 and July 2017, 158 participants who were on a combination of DTG/ABC/3TC for a median of 9 months (interquartile range [IQR], 4–14) were randomized to either receive DTG monotherapy (n = 78) or to continue DTG/ABC/3TC (n = 80) as a fixed-dose combination (Figure 1). All received at least 1 dose of study treatment. The mITT and PP populations consisted of 153 and 146 participants, respectively (Figure 1). Baseline characteristics were well balanced between the 2 study arms (Table 1).

Primary Endpoint

At week 24, proportions of participants with HIV RNA <50 copies/mL in the DTG and DTG/ABC/3TC arms were, respectively, 93.6% (73/78) and 96.3% (77/80) in the ITT analysis (difference, 2.7%; 95% CI, −5.0 to 10.8); 97.3% (73/75) and 98.7% (77/78) in mITT analysis (difference, 1.4%; 95% CI, −4.5 to 8.1); 97.1% (67/69); and 98.7% (76/77) in PP analysis (difference, 1.6%; 95% CI, −4.5 to 8.8), meeting prespecified criteria for noninferiority (Figure 2A and 2B). Two participants in the DTG arm experienced protocol-defined VF at week 24; both had low-level viremia (84 copies/mL on first sample, 63 copies/mL on confirmatory sample; 55 and 51 copies/mL, respectively) and their HIV RNA returned to <50 copies/mL at week 36 after treatment intensification. One participant in the DTG/ABC/3TC arm switched antiretrovirals at week 4 for

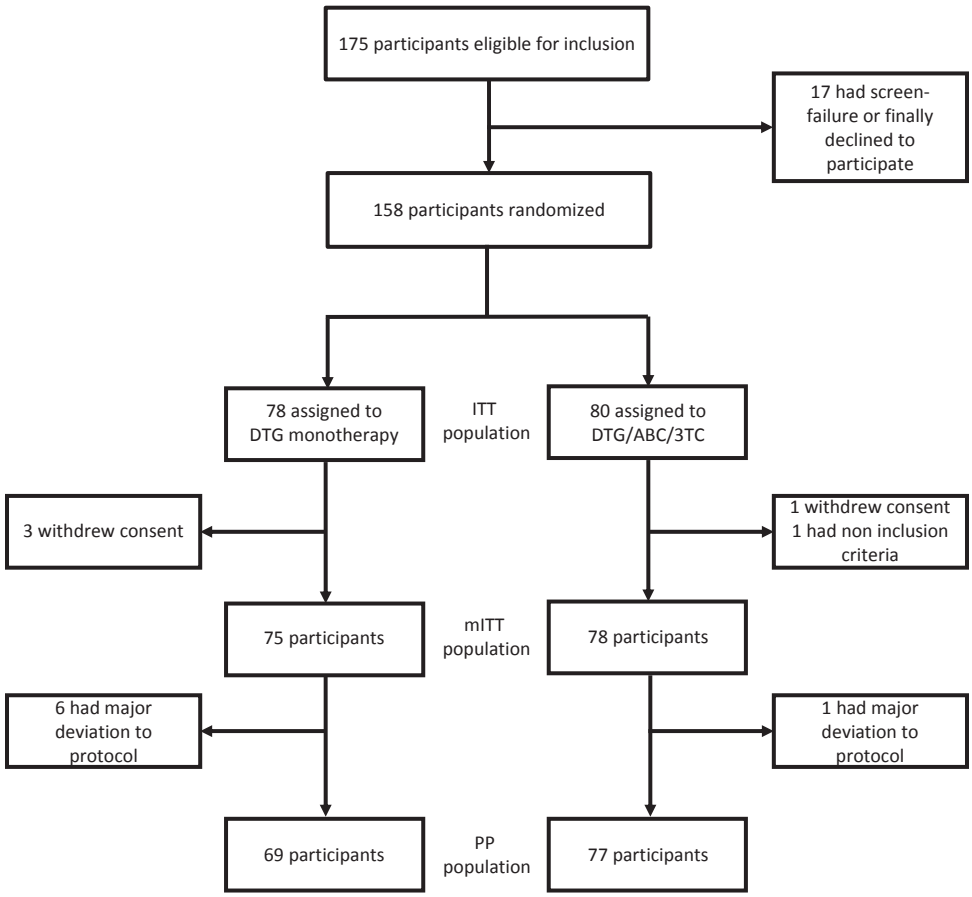

Figure 1. Trial profile. Abbreviations: 3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per-protocol.

Table 1. Demographic and Baseline Characteristics

Characteristic	Dolutegravir Arm (n = 78)	Dolutegravir/Abacavir/Lamivudine Arm (n = 80)
Age (years)	47 (40–54)	48 (41–58)
Male	58 (74%)	56 (70%)
Center for Diseases Control stage C	4 (5%)	2 (3%)
Nadir CD4 (cells/μL)	309 (215–415)	265 (198–377)
Zenith HIV RNA (log_{10} copies/mL)	4.9 (4.4–5.4)	4.8 (4.1–5.3)
Time since HIV diagnosis (years)	9 (4–18)	11 (6–19)
Duration on cART (years)	8 (3–15)	9 (5–17)
Previous lines of cART	4 (3–7)	5 (3–7)
Previous exposition to raltegravir and/or elvitegravir	13 (17%)	23 (29%)
Current CD4 count (cells/μL)	843 (669–1030)	790 (601–996)
Presence of a polymerase chain reaction signal[a]	22 (28%)	20 (25%)

Variables are expressed as n (%) or median (interquartile range).

Abbreviations: cART, combined antiretroviral therapy; HIV, human immunodeficiency virus.

[a]A detectable but not quantifiable plasma HIV RNA.

a drug-related adverse event (AE; mood disturbance). After reviewing week 24 results, the DSMB indicated that the study could continue to week 48, as initially planned.

Between week 24 and week 48, 3 additional participants experienced VF, 2 at week 36 and 1 at week 48, all in the DTG arm. After the occurrence of these 5 VFs, the DSMB met once again on 21 December 2017. The sponsor decided to stop the experimental arm (DTG monotherapy), following DSMB recommendations and in accordance with the prespecified stopping rule. All participants in the DTG arm who had not completed the week 48 visit (n = 8) were immediately recalled for an HIV RNA control before treatment reintensification. At that time, 2 additional participants had HIV RNA above 50 copies/mL: 604 copies/mL (corresponding to week 29) and 626 copies/mL (corresponding to week 48), respectively.

Overall, 7 participants experienced VF in the DTG arm, whereas there were none in the DTG/ABC/3TC arm (Figure 3). Characteristics of participants with VFs are summarized in Table 2.

Secondary Endpoints

Amplification of integrase gene in plasma was successful at peak viremia for all 7 cases of VF, of whom 2 harbored a virus with emergence of resistance mutations to the INSTI class (Table 2). Both patients had integrase wild-type virus in historical genotype RNA prior to the study and in genotype DNA at the screening visit. All participants with VF self-declared high adherence rate before and at the time of VF (median, 100%; IQR, 95–100) and had no concomitant medication that could cause negative drug–drug interaction with DTG. All 7 patients had their HIV RNA rapidly resuppressed below 50 copies/mL after treatment intensification with DTG/ABC/3TC (n = 4) or DTG/3TC (n = 1) in the 5 patients with no INSTI mutation and with ritonavir-boosted darunavir plus ABC/3TC in the 2 patients with INSTI mutations.

At week 48, changes from baseline regarding CD4 counts and CD4:CD8 ratio were not different between arms.

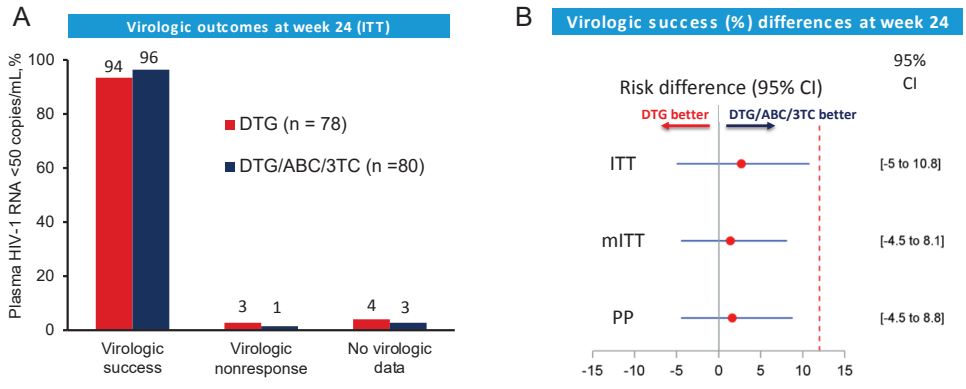

Figure 2. Primary outcomes at 24 weeks. *A*, Proportions of participants with virologic success (plasma HIV RNA <50 copies/mL), virologic nonresponse, and no virologic data (snapshot analysis in the ITT population). *B*, Differences (triple minus monotherapy) and 95% CI in the proportions of participants with virologic success (snapshot analyses in the ITT, mITT, and PP populations). Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; DTG, dolutegravir; HIV, human immunodeficiency virus; ITT, intention-to-treat; mITT, modified intention-to-treat; PP, per-protocol.

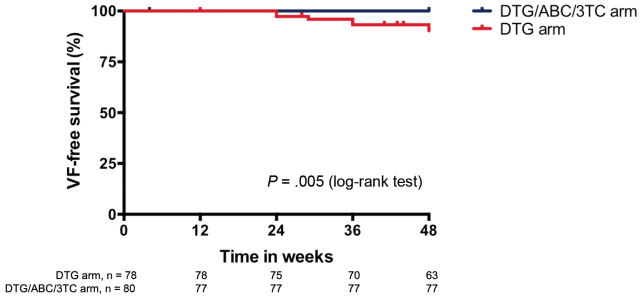

Figure 3. Virologic success, by treatment arm. Kaplan–Meier curve showing the proportion (%) of VF–free estimates from randomization to week 48 visit, according to the randomly assigned treatment arm. Abbreviations: 3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; VF, virologic failure.

During the 48 weeks of the study, all grades and causalities of AEs were reported in 73.1% of the participants in the DTG monotherapy arm and in 81.3% in the DTG/ABC/3TC arm, of whom 6 (10.5%) and 8 (12.3%) were related to study drugs, respectively (Table 3). One participant in the DTG/ABC/3TC arm discontinued study drugs for an AE (grade 2 mood disturbance). Serious AEs (SAEs) occurred less frequently, although not significantly, in the DTG arm (6.4%) compared with the DTG/ABC/3TC arm (16.3%; $P = .08$). One SAE was possibly related to study drugs in each arm (spontaneous abortion and grade 4 creatine kinase elevation in the DTG and DTG/ABC/3TC arms, respectively); none led to treatment discontinuation. No deaths or AIDS-defining events occurred during the study. Grade 3 or 4 laboratory AEs were observed in 11.5% of patients in the DTG arm and 8.8% in the DTG/ABC/3TC arm ($P = .61$).

At week 48, changes from baseline regarding eGFR, total cholesterol, HDL cholesterol, and LDL cholesterol were not different between arms.

DISCUSSION

The MONCAY trial demonstrated that DTG monotherapy was not a valid option to maintain virological suppression over time in PLHIV with chronic infection on a successful DTG/ABC/3TC regimen, even though it met noninferiority to DTG/ABC/3TC at week 24. Indeed, DTG monotherapy led to a high incidence of VFs between week 24 and week 48, with a cumulative incidence of 9.7% (95% CI, 2.8 to 16.6) at week 48. In the time-to-event analysis (Figure 3), the risk of virological failure was significantly higher in the DTG arm compared with the DTG/3TC/ABC arm, both clinically and statistically [2, 3]. Moreover, it favored the emergence of INSTI resistance that severely compromised the further use of the class. In contrast, no VF occurred in patients who continued DTG/ABC/3TC. In addition, DTG monotherapy was only associated with a marginal safety advantage; despite a higher rate of SAEs on the triple arm, discontinuation for AEs occurred rarely and with no differences between arms.

Our findings are consistent with results of the DOMONO trial, the first randomized trial to evaluate DTG monotherapy as a maintenance strategy after various triple therapies [14]. The authors also reported noninferiority at week 24 whereas expanded follow-up showed additional VFs that led to premature study termination. Overall, 8 of 95 (8%) participants in DOMONO experienced VF, 3 of whom were found to have emergent mutations for the INSTI class [18]. Of note, our study enrolled more patients than DOMONO, as we designed the study with 90% power to demonstrate noninferiority compared with 80% power in DOMONO, and we prolonged follow-up of randomized groups until week 48, while in DOMONO, the outcome of DTG monotherapy between week 24 and week 48 was compared with a nonrandomized contemporary group.

During the last decade, monotherapy has been extensively investigated with bPI; ritonavir-boosted lopinavir, darunavir, and atazanavir were challenged as a maintenance therapy after a suppressive triple therapy. Overall, in a metaanalysis, bPI monotherapies also resulted in a higher risk of cumulative VFs compared with triple-therapy continuation [9]. However, in contrast to DTG monotherapy, there was no increased risk of class-emergent mutations at VF with bPI. Therefore, even though bPI monotherapy was not noninferior to triple therapy in the primary switch-equals-failure analysis, noninferiority

Table 2. Characteristics of Virologic Failures in the Dolutegravir Arm

Participant No.	Week at VF	CD4 Nadir (Cells/μL)	Prior Exposure to First-generation INSTI (Drug)	cART Duration Before Dolutegravir Monotherapy (Years)	Self-Reported Adherence at Week 4 (%)	Peak Human Immunodeficiency Virus RNA (Copies/mL)	Integrase Sequencing at VF
1	24	231	No	11	100	84	No mutation
2	24	163	No	10	100	55	No mutation
3	29	197	Yes (raltegravir)	5	95	604	No mutation
4	36	252	No	19	100	46 300	S147G, N155H
5	36	200	No	2	95	110	No mutation
6	48	119	No	21	95	2230	R263K[a]
7	48	118	No	4	100	626	No mutation

Abbreviations: cART, combined antiretroviral therapy; INSTI, integrase strand transfer inhibitor; VF, virologic failure.

[a]Participant 6 also had a mutation in the 3′ PPT region (G replaced by A in position 9076); its impact on resistance is currently unknown.

Table 3. Adverse Events

Events	Dolutegravir Arm (n = 78)	Dolutegravir/Abacavir/Lamivudine Arm (n = 80)	*P* Value
Participant with any AE	57 (73.1)	65 (81.3)	.26
AE related to study drug	6 (7.7)	8 (10.0)	.78
AE leading to trial discontinuation[a]	0	1 (1.3)	1
Participant with any SAE	5 (6.4)	13 (16.3)	.08
All SAEs	5 (6.4)	15 (18.8)	.03
SAE related to study drug[b]	1 (1.3)	1 (1.3)	1
SAE leading to trial discontinuation	0	0	…
Any grade 3–4 laboratory abnormality	9 (11.5)	7 (8.8)	.61

Variables are expressed as n (%).

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a]Dolutegravir/abacavir/lamivudine arm: mood disturbance, discontinuation at week 4.

[b]Dolutegravir/abacavir/lamivudine arm: grade 4 creatine kinase elevation; dolutegravir arm: spontaneous abortion.

was reached in the intensification-included analysis where suppressive intensification with triple therapy was counted as success. Noteworthy, all participants who experienced VF during MONCAY (n = 7) and DOMONO (n = 8) were rapidly resuppressed after treatment intensification, which consisted of resuming the previous triple regimen in most cases (n = 12), adding a single nucleosidic reverse transcriptase inhibitor (NRTI; n = 1), or resuming the same 2 NRTIs while switching the third agent (from DTG to boosted darunavir, n = 2) [18].

In contrast with DTG-based triple therapy where emergence of resistance mutation has only rarely occurred in case of VF in INSTI-naive patients [19, 20], INSTI mutations were reported as soon as DTG was used as a monotherapy, first in observational cohorts then in randomized trials [14, 18, 21–27]. A wide set of mutations have been described in this setting (E92Q, T97A, G118R, E138K, G140A/S, S147G, Q148K/H/R, N155H, S230R, R263K), some of which have not been described before DTG monotherapy [18, 27, 28]. These mutations were detected at various times of DTG monotherapy (ranging from 4 to 60 weeks) and whatever the patients were previously naive of INSTI, exposed to first generation of INSTI (raltegravir or elvitegravir) or DTG-based triple therapy. In most cases, these mutations were likely emerging as patients were INSTI naive and/or had evidence of wild-type virus (in HIV-1 RNA and/or DNA) before initiating DTG monotherapy. Additionally, mutations outside the integrase gene (in the 3' PPT region) were recently described, both in vitro and ex vivo (from a failing participant in DOMONO who had no INSTI mutation) that conferred resistance to all currently used INSTIs [18, 29]. In MONCAY we also described a participant with VF who had a mutation in the 3' PPT region (G replaced by A in position 9076). Its impact on resistance is currently unknown and under further investigation. In contrast to the one reported in DOMONO, our mutation was found in addition to the R263K that already conferred resistance to all INSTIs. Together, results from monotherapy studies suggest that the genetic barrier to DTG is not optimal and that such use should be definitively discouraged. This is of major clinical relevance, given the high importance of DTG in today's antiretroviral armamentarium and the high efficacy and barrier to resistance when used in combination with 1 or 2 other antiretrovirals. In a recent meta-analysis that included 8 studies where participants (n = 251) were switched to DTG monotherapy and 14 studies where participants (n = 1670) were switched to DTG-based dual therapies, the incidence of VF was 8.9% (95% CI, 4.7–16.2) vs 0.7% (95% CI, 0.4–1.3) at week 48, respectively [28]. Importantly, 9 of 16 (56%) participants with VF developed INSTI mutations in the DTG monotherapy group, whereas there were none in the DTG-based dual therapy group.

The mechanism(s) that lead to VF during DTG monotherapy remains unclear. In the 2 randomized trials where participants were highly selected and long-term suppressed, there was neither evidence of poor adherence to the treatment, as assessed by self-reported questionnaires and DTG concentration at failure, nor potential drug–drug interactions [14]. In MONCAY, as participants were naive of INSTI or had never failed while on an INSTI-based triple therapy and had no evidence of any INSTI mutation at baseline, it is unlikely that DTG monotherapy selected a dominant virus resistant to INSTI. Nevertheless, only ultradeep sequencing detects minority variants, and these tests were not performed at baseline. In this regard, Wijting et al proposed that a stochastic reactivation of a single cell harboring a preexistent provirus containing INSTI mutations could lead to VF [18]. Inhibiting HIV replication with only 1 antiretroviral has consistently led to increased risk of VF and emergence of resistance, and DTG is no exception to this rule. Other mechanisms could be involved, such as low DTG concentrations in sanctuaries, in particular with lymph nodes, leading to suboptimal inhibition of viral replication in this compartment [30]. It has also been suggested that a lower CD4 nadir and a higher HIV-1 DNA load in peripheral blood mononuclear cells are associated with VF [31].

We are aware of limitations to our study. First, the study was open label. Second, a 12% noninferiority margin could be viewed as too large compared with current methodological standards. Third, one advantage of less-drug regimens over triple therapy is to reduce toxicity and costs [7, 32, 33], but the short follow-up we provided was unlikely to show significant differences between treatment arms, if any. Fourth, our inclusion criteria did not specify markers of viral reservoir, such as HIV-DNA, which may influence the efficacy of maintenance strategies.

A main lesson from monotherapy studies (including ours) is that a short-term endpoint (ie, 24 weeks) is certainly not predictive of sustained virological suppression. HIV infection is a lifelong disease that requires a lifelong antiretroviral efficacy. Our study perfectly illustrates that no definitive conclusion or change in clinical practice should be made based on short-term results, especially for new combinations and/or less-drug regimens. Durability of virologic suppression should become an essential prerequisite before changing the paradigm of antiretroviral therapy.

In conclusion, this 48-week, randomized, controlled study provides evidence that DTG monotherapy confers high risk of VF and of emergence of INSTI resistance. Therefore, this strategy should be definitely abandoned among people living with chronic HIV infection.

Notes

List of all contributors (MONCAY study group). Olivier Bollengier-Stragier, Jean-Luc Esnault, Thomas Guimard, Sophie Leautez, Philippe Perré (La Roche-sur-Yon); Romain Lemarie, Xavier Pouget-Abadie, Mariam Roncato-Saberan (La Rochelle); Marie André, Thierry May, Evelyne Schvoerer (Nancy); Clotilde Allavena, Elisabeth Andre-Garnier, Camille Bernaud, Eric Billaud, Sabelline Bouchez, Nolwenn Hall, François Raffi, Véronique Reliquet, Florian Vivrel (Nantes); Pascale Deleplanque, Anabele Dos-Santos, Simon Sunder (Niort); Cendrine Boulard, Aurélie Despujols, Jérôme Guinard, Laurent Hocqueloux, Sandrine Lefeuvre, Catherine Mille, Mohamadou Niang, Montasser Ouezzani, Thierry Prazuck, Gaëlle Thomas, Antoine Valéry (Orléans); Véronique Avettand-Fènoël (Paris); Geneviève Giraudeau, Gwenaël Le Moal (Poitiers); Marie-Laure Batard, Samira Fafi-Kremer, David Rey (Strasbourg); Francis Barin, Frédéric Bastides, Louis Bernard, Guillaume Gras, Marie Charlotte Hallouin-Bernard, Adrien Lemaignen, Pascal Le Bret, Karl Stefic (Tours).

Acknowledgments. The authors warmly thank all patients and staff who participated in the study, and members of the Data Safety Monitoring Board (Etienne Audureau, Sébastien Gallien, and Jean-Christophe Plantier).

Disclaimer. The funder had no role in the study design, data analysis and interpretation, or manuscript writing. All authors had full access to the data and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Financial support. The MONCAY trial was funded by the Centre Hospitalier Régional d'Orléans–La Source (Orléans, France) with support of the COREVIH Centre-Poitou Charentes (Tours, France).

Potential conflicts of interest. L. H. reports personal fees and nonfinancial support from Gilead Sciences, Janssen, Merck, and ViiV Healthcare outside the submitted work. F. R. reports personal fees from Gilead, Janssen, Merck, and ViiV Healthcare outside the submitted work. S. S. reports personal fees and nonfinancial support from Gilead and nonfinancial support from Janssen and ViiV Healthcare outside the submitted work. D. R. reports nonfinancial support from Gilead, Abbvie, BMS, and ViiV Healthcare outside the submitted work. E. B. reports personal fees from Janssen, Gilead, ViiV Healthcare, MSD, and Mylan outside the submitted work. V. A.-F. reports nonfinancial support from Janssen and ViiV Healthcare outside the submitted work. J.-J. P. reports grants and personal fees from ViiV Healthcare and MSD and personal fees from Gilead outside the submitted work. C. A. reports personal fees and nonfinancial support from Janssen, ViiV Healthcare, Merck, and Gilead and personal fees from Mylan outside the submitted work. All remaining authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Lundgren JD, Babiker AG, Gordin F, et al; INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med **2015**; 373:795–807.
2. 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.
3. EACS Guidelines version 8.2. **2017**. Available at: http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Accessed 20 August 2017.
4. Arribas JR, Girard PM, Landman R, et al; OLE/RIS-EST13 Study Group. Dual treatment with lopinavir-ritonavir plus vudine versus triple treatment with lopinavir-ritonavir plus vudine 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.
5. Perez-Molina JA, Rubio R, Rivero A, et al; GESIDA 7011 Study Group. Dual treatment with atazanavir-ritonavir plus vudine 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.
6. Di Giambenedetto S, Fabbiani M, Quiros Roldan E, et al; Atlas-M Study Group. Treatment simplification to atazanavir/ritonavir + vudine 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.
7. 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.
8. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus vudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet **2019**; 393:143–55.
9. 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.
10. Kandel CE, Walmsley SL. Dolutegravir—a review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther **2015**; 9:3547–55.
11. Patel DA, Snedecor SJ, Tang WY, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One **2014**; 9:e105653.
12. Gubavu C, Prazuck T, Niang M, et al. Dolutegravir-based monotherapy or dual therapy maintains a high proportion of viral suppression even in highly experienced HIV-1-infected patients. J Antimicrob Chemother **2016**; 71:1046–50.
13. HIV-1 genotypic drug resistance interpretation's algorithms. Available at: http://www.hivfrenchresistance.org/2018/tab6.html. Accessed 21 August 2018.
14. Wijting I, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV (DOMONO): a phase 2, randomised non-inferiority trial. Lancet HIV **2017**; 4:e547–54.
15. Parienti JJ, Verdon R, Massari V. Methodological standards in non-inferiority AIDS trials: moving from adherence to compliance. BMC Med Res Methodol **2006**; 6:46.
16. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA **2012**; 308:2594–604.
17. Blanco JL, Oldenbuettel C, Thomas R, et al. Pathways of resistance in subjects failing dolutegravir monotherapy. In: CROI Conference. Available at: http://www.croiconference.org/sessions/pathways-resistance-subjects-failing-dolutegravir-monotherapy. Accessed 17 November 2018.

18. Wijting IEA, Lungu C, Rijnders BJA, et al. HIV-1 resistance dynamics in patients with virologic failure to dolutegravir maintenance monotherapy. J Infect Dis **2018**; 218:688–97.
19. Lepik KJ, Harrigan PR, Yip B, et al. Emergent drug resistance with integrase strand transfer inhibitor-based regimens. AIDS **2017**; 31:1425–34.
20. Fulcher JA, Du Y, Zhang TH, Sun R, Landovitz RJ. Emergence of integrase resistance mutations during initial therapy containing dolutegravir. Clin Infect Dis **2018**; 67:791–4.
21. Rokx C, Schurink CA, Boucher CA, Rijnders BJ. Dolutegravir as maintenance monotherapy: first experiences in HIV-1 patients. J Antimicrob Chemother **2016**; 71:1632–6.
22. Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. J Antimicrob Chemother **2016**; 71:1948–53.
23. Rojas J, Blanco JL, Marcos MA, et al. Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression. J Antimicrob Chemother **2016**; 71:1975–81.
24. Katlama C, Soulié C, Caby F, et al. Dolutegravir as monotherapy in HIV-1-infected individuals with suppressed HIV viraemia. J Antimicrob Chemother **2016**; 71:2646–50.
25. Oldenbuettel C, Wolf E, Ritter A, et al. Dolutegravir monotherapy as treatment de-escalation in HIV-infected adults with virological control: DoluMono cohort results. Antivir Ther **2017**; 22:169–72.
26. Blanco JL, Rojas J, Paredes R, et al; DOLAM Study Team. Dolutegravir-based maintenance monotherapy versus dual therapy with vudine: a planned 24 week analysis of the DOLAM randomized clinical trial. J Antimicrob Chemother **2018**; 73:1965–71.
27. Blanco JL, Marcelin AG, Katlama C, Martinez E. Dolutegravir resistance mutations: lessons from monotherapy studies. Curr Opin Infect Dis **2018**; 31:237–45.
28. Wandeler G, Buzzi M, Anderegg N, et al. Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: systematic review and meta-analysis. F1000Res **2018**; 7:1359.
29. Malet I, Ambrosio FA, Subra F, et al. Pathway involving the N155H mutation in HIV-1 integrase leads to dolutegravir resistance. J Antimicrob Chemother **2018**; 73:1158–66.
30. Fletcher CV, Thorkelson A, Winchester L, et al. Comparative lymphoid tissue pharmacokinetics (PK) of integrase inhibitors (INSTI). In: CROI Conference. Available at: http://www.croiconference.org/sessions/comparative-lymphoid-tissue-pharmacokinetics-pk-integrase-inhibitors-insti. Accessed 3 September 2018.
31. Wijting I, Rutsaert SL, Rokx C, et al. Predictors of virological failure in HIV-1-infected patients switching to dolutegravir maintenance monotherapy. HIV Med **2019**; 20:63–8.
32. Wijting I, Rokx C, Smits SA, et al. Bone, renal, and inflammation markers in the dolutegravir monotherapy (DOMONO) study. In: CROI Conference. Available at: http://www.croiconference.org/sessions/bone-renal-and-inflammation-markers-dolutegravir-monotherapy-domono-study. Accessed 3 September 2018.
33. Baril JG, Angel JB, Gill MJ, et al. Dual therapy treatment strategies for the management of patients infected with HIV: a systematic review of current evidence in ARV-naive or ARV-experienced, virologically suppressed patients. PLoS One **2016**; 11:e0148231.