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MAJOR ARTICLE

Noninferiority of Simplified Dolutegravir Monotherapy Compared to Continued Combination Antiretroviral Therapy That Was Initiated During Primary Human Immunodeficiency Virus Infection: A Randomized, Controlled, Multisite, Open-label, Noninferiority Trial

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(See the Major article by Hocqueloux et al on pages 1498-505 and Editorial Commentary by Rijnders and Rokx on pages 1506–8.)

Background. Patients who start combination antiretroviral therapy (cART) during primary human immunodeficiency virus type 1 (HIV-1) infection show a smaller HIV-1 latent reservoir, less immune activation, and less viral diversity compared to patients who start cART during chronic infection. We conducted a pilot study to determine whether these properties would allow sustained virological suppression after simplification of cART to dolutegravir monotherapy.

Methods. EARLY-SIMPLIFIED is a randomized, open-label, noninferiority trial. Patients who started cART <180 days after a documented primary HIV-1 infection and had an HIV-1 RNA <50 copies/mL plasma for at least 48 weeks were randomized (2:1) to monotherapy with dolutegravir 50 mg once daily or to continuation of cART. The primary efficacy endpoint was the proportion of patients with <50 HIV-1 RNA copies/mL on or before week 48; noninferiority margin 10%.

Results. Of the 101 patients randomized, 68 were assigned to simplification to dolutegravir monotherapy and 33 to continuation of cART. At week 48 in the per-protocol population, 67/67 (100%) had virological response in the dolutegravir monotherapy group vs 32/32 (100%) in the cART group (difference, 0.00%; 95% confidence interval, −100%, 4.76%). This showed noninferiority of the dolutegravir monotherapy at the prespecified level.

Conclusion. In this pilot study consisting of patients who initiated cART during primary HIV-1 infection and had <50 HIV-1 RNA copies/mL for at least 48 weeks, monotherapy with once-daily dolutegravir was noninferior to cART. Our results suggest that future simplification studies should use a stratification according to time of HIV infection and start of first cART.

Clinical Trials Registration. NCT02551523.

Keywords. primary HIV infection; dolutegravir; monotherapy; simplification; randomized controlled trial.

Long-term toxicity of combination antiretroviral therapy (cART) is a substantial contributor to morbidity in chronically infected human immunodeficiency virus type 1 (HIV-1)–positive individuals [1]. Nucleoside reverse transcriptase inhibitors (NRTIs) are the main reason for ART-related toxicity. Trying to avoid NRTIs, initial randomized studies explored protease inhibitor–based monotherapy strategies. From a virological point of view, protease inhibitor–based monotherapy was clearly inferior to cART and was therefore not introduced into clinical practice [2]. However, at least in the context of more frequent viral load monitoring in a clinical trial, it did not lead to the loss of more treatment options compared to cART [3].

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) used as a component of preferred cART [4]. Several simplification studies were recently performed with dolutegravir as a main active drug [5, 6]. A dolutegravir-based dual-therapy regimen in combination with lamivudine or rilpivirine shows promising results [5, 7]. In contrast, 3 randomized, controlled trials that explored the efficacy of dolutegravir-based monotherapy revealed inferiority compared to cART [6, 8, 9]. Notably, all protease inhibitor and dolutegravir simplification studies were conducted in patients initiating cART during chronic HIV-1 infection. Importantly, patients who initiated cART during the early phase of

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HIV-1 infection harbor a markedly reduced HIV-1 reservoir [10, 11] and show low levels of viral diversity [12, 13].

The Zurich Primary HIV Infection Study (ZPHI) is an ongoing observational study enrolling individuals with documented primary HIV infection, that is, individuals identified within 180 days after estimated date of infection [14]. Since 2002, immediate start of cART is offered to the ZPHI participants. We hypothesized that individuals who start cART early have a smaller HIV-1 reservoir and, therefore, are the best candidates to maintain viral suppression after switching to dolutegravir monotherapy comparable to that seen under continued cART.

We tested our hypothesis in a pilot study consisting of individuals who had been successfully treated with cART for at least 48 weeks since primary HIV-1 infection before being randomized to dolutegravir monotherapy.

METHODS

Study Design and Patients

All patients enrolled in this trial have a documented primary HIV-1 infection, and the majority of them (85%) are enrolled in the ZPHI, an open-label, nonrandomized, observational, multisite study (NCT02551523) [14]. All patients were participating in the Swiss HIV cohort study, a long-term observational study [15]. Primary HIV-1 infection was defined as published elsewhere [16].

In this randomized, open-label, noninferiority trial, we recruited patients aged ≥18 years with a primary HIV-1 infection and no previous antiretroviral treatment failure, no prior treatment interruption, no major resistance mutations to INSTIs according to the Stanford algorithm [17], an HIV-1 RNA of less than 50 copies/mL plasma for 48 weeks or longer, and a negative hepatitis B virus surface antigen. Patients with documented resistance to any NRTI, non-NRTI, or protease inhibitors were allowed to be included. Exclusion criteria were pregnancy or breastfeeding, use of contraindicated drugs to dolutegravir, and previous intolerance to dolutegravir.

We obtained ethics committee approval at all participating centers in accordance with the principles of the 2008 Declaration of Helsinki. All participants gave their written informed consent before undergoing any study procedure.

Study Procedures

Patients in the monotherapy group were simplified to oral dolutegravir 50 mg once daily, and those in the cART group continued their current regimen consisting of an INSTI, a boosted protease inhibitor, or non-NRTI, in combination with 2 NRTIs. We assessed HIV-1 RNA in plasma using the COBAS AmpliPrep/TaqMan HIV-1 Test Vs 2.0 with a limit of detection ≤20 HIV-1 RNA copies/mL plasma. We measured total HIV-1 DNA in peripheral blood mononuclear blood cells (PBMCs) using an in-house digital droplet polymerase chain reaction assay at baseline and week 48. We assessed markers for proximal renal tubulopathy and lipid levels at baseline and at week 48. All patients were asked for a lumbar puncture at baseline and at week 48. ART drug levels were measured in plasma and in cerebrospinal fluid (CSF) at week 0 and week 48. The study procedures are described in detail in the Supplementary Materials.

Outcomes

The primary endpoint was noninferiority of the virological response between treatment groups, defined as the proportion of patients without a virological failure on or before week 48. Virological failure was defined as 2 consecutive viral loads (14 days or longer but not more than 30 days apart) above 50 HIV-1 RNA copies/mL plasma. The window of visit was ±4 weeks, thus an HIV-RNA value obtained between week 44 and week 52 was included in the primary efficacy analysis. If the HIV-1 RNA measurement was missing at week 48, we included the last documented HIV-1 RNA measurement prior to week 48 in the primary efficacy analysis (last observation carried forward principle).

Secondary endpoints were quantification of total HIV-1 DNA in PBMCs, central nervous system (CNS) virological escape (defined as less than 40 HIV-1 RNA copies/mL CSF), frequency of blips (defined as 1 viral load between 50 and 400 followed by a viral load below 50 HIV-1 RNA copies/mL plasma within 30 days), number of adverse events and serious adverse events, changes in CD4 cell count, new onset of proximal tubular renal dysfunction (defined as pathological tubulopathy markers according to Fux et al [18]), changes in lipid profiles, withdrawing consent and lost to follow-up and switching assigned treatment for any cause before and after simplification.

Statistical Analyses

The study was powered to detect noninferiority at 48 weeks, assuming a response of 95% in both groups. Thus, to show noninferiority at a margin of 10% at week 48, with a significance value of 5% and a power of 80%, we estimated the sample size at 138 assessable patients. The final study population consisted of 101 patients because of the lower rate of recruitment as anticipated during the last few months of the study. The decision to stop recruitment was taken by the sponsor (H.F.G.) and was independent of any efficacy analysis. The static unstratified multiblock randomization with multiplier 3 integrated in SecuTrial was used to allocate patients in a 2:1 ratio to monotherapy with dolutegravir or continuation of cART including 3 patients per block with computer-generated random number sequences. More details are provided in the Supplementary Materials.

RESULTS

Of 430 patients assessed for study enrollment, 101 (23.4%) were eligible for the study and agreed to participate (Figure 1). Between 30 November 2015 and 10 March 2017, we randomized 101 patients in a 2:1 ratio, allocating 68 (67%) to dolutegravir

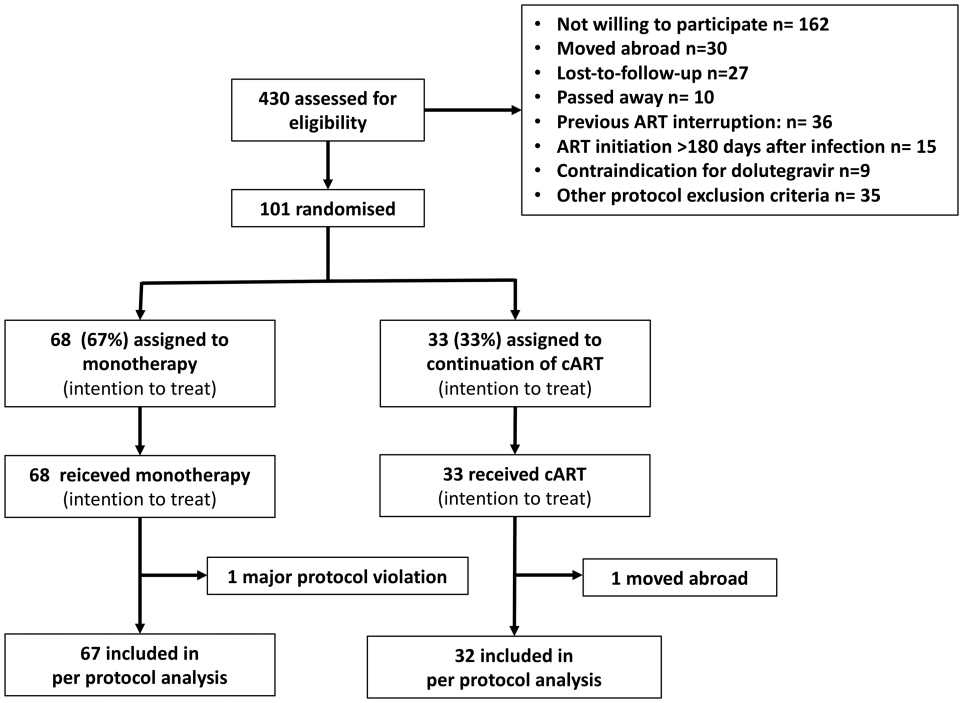

Figure 1. Trial profile. Abbreviation: cART, combination antiretroviral therapy.

monotherapy and 33 (33%) to cART (Figure 1). Baseline characteristics are depicted in Table 1.

Efficacy

In the per-protocol population, all 67 patients in the monotherapy group and all 32 patients in the cART group had a virological response on or before week 48 (Figure 2). One patient in the monotherapy group was excluded during the study due to a major protocol violation. This patient did not fulfill the definition of a primary HIV-1 infection; however, this information was missed at screening, and the patient was therefore incorrectly enrolled into the study. Detailed information on this patient is provided in the Supplementary Materials. In the cART group, 1 patient moved abroad at week 26 (Figure 1). Noninferiority was shown at the prespecified level of 10%, as the difference in efficacy between monotherapy and cART was similar. We also noted noninferiority in the intention-to-treat population (67/68, 98.5% dolutegravir versus 33/33, 100% cART; difference 1.47%, 95% CI [–100%, 6.85%]). The patient in the cART group who moved abroad was counted as success in the intention-to-treat analysis, assuming that this patient maintained viral suppression after study discontinuation. This assumption led to a more conservative approach in interpreting the data.

HIV-1 Reservoir

We measured total HIV-1 DNA in PBMCs at baseline and at week 48. The median $\log_{10}$ total HIV-1 DNA change from baseline to week 48 in the dolutegravir monotherapy arm was –0.16 compared to –0.10 in the cART arm (P = .312; Figure 3). There was a significant decay of the total HIV DNA in the monotherapy arm at week 48 compared to baseline (P = .0004). The HIV DNA decay among the cART group did not reach statistical significance (P = .0982). The total HIV-1 DNA levels for single patients are shown in Supplementary Figure 1. We recorded viral load blips that did not lead to treatment interruption in 1 (1.5%) of 68 patients in the monotherapy group (607 visits) and 1 (3.0%) of 33 patients (124 visits) in the cART group (P < .001 from the Poisson regression for rate of blips; Figure 4). The median change in CD4 cell count from baseline was 74 cells/μL blood (interquartile range [IQR], –32 to 198) for monotherapy and 24 cells/μL blood (IQR, –144 to 116) for cART (P = .124) (Supplementary Figure 2). All patients in both study groups were adherent to study drugs for the 48 weeks of study.

Plasma and CSF Dolutegravir Levels Assessment

At baseline, 23 (33.8%) patients in the monotherapy group and 14 (42.4%) in the cART group agreed to have a lumbar puncture. At week 48, 10 (14.9%) patients in the monotherapy group and 2 (6.2%) in the cART group agreed to have a second lumbar puncture. The CSF viral load was undetectable in all sampled patients at all times tested (Figure 5). Plasma and CNS concentration of dolutegravir measurements at weeks 0, 4, and 48 are depicted in Figure 6. According to the percentile curves of Aouri et al [19], 3.7% (n = 6) of dolutegravir concentrations in

Table 1. Baseline Characteristics of Study Participants

Characteristic	Overall (N = 101)	Monotherapy (n = 68)	Combination ART (n = 33)
Age (y)	42 (33–47)	42 (33–47)	43 (35–46)
Male (%)	97 (96.0)	65 (95.6)	32 (97.0)
Ethnicity (%)			
White	93 (92.1)	62 (91.2)	31 (93.9)
Black	5 (5.0)	4 (5.9)	1 (3.0)
Asian	2 (2.0)	2 (2.9)	0 (0.0)
Hispanic	1 (1.0)	0 (0.0)	1 (3.0)
HIV transmission risk (%)			
Men who have sex with men	84 (83.2)	56 (82.4)	28 (84.8)
Heterosexual	15 (14.9)	10 (14.7)	5 (15.2)
Other	2 (2.0)	2 (2.9)	0 (0.0)
HIV-1 subtype (%)			
B	63 (62.4)	44 (64.7)	19 (57.6)
CRF01_AE	8 (7.9)	5 (7.4)	3 (9.1)
CRF02_AG	5 (5.0)	1 (1.5)	4 (12.1)
Other	17 (17.0)	11 (10.0)	6 (18.0)
NA	8 (7.9)	7 (10.3)	1 (3.0)
Body mass index (kg/m^2)	23.8 (22.4–26.6)	23.7 (22.1–26.2)	24.2 (22.5–27.4)]
Fiebig stage (%)			
I–II	2 (2.0)	1 (1.5)	1 (3.0)
II–III	21 (20.8)	16 (23.5)	5 (15.2)
IV–VI	58 (57.4)	36 (52.9)	22 (66.7)
NA	20 (20.0)	15 (22.0)	5 (15.0)
Days from infection until ART start	38 (28–77)	39 (27–73)	36 (29–113)
Years on ART before study entry	3.6 (2.0–6.0)	3.8 (1.9–6.1)	3.3 (2.0–5.5)
Nadir CD4 cell count (cells/μL)	358 (265–486)	376 (263–496)	329 (269–442)
CD4 cell count (cells/μL)	716 (584–918)	730 (610–920)	669 (545–881)
Integrase strand transfer inhibitor–based regimen (%)	55 (54.5)	40 (58.8)	15 (45.5)
Dolutegravir-based regimen (%)	46 (45.5)	33 (48.5)	13 (39.4)
Backbone regimen (%)			
Abacavir based	28 (27.7)	22 (32.4)	6 (18.2)
Tenofovir based	69 (68.3)	46 (67.6)	23 (69.7)
Other	4 (4.0)	0 (0.0)	4 (12.1)
Number of VL measurements during 48 weeks before study	3 (3–4)	3 (3–4)	4 (3–4)
Rate of VL monitoring under ART before study (values/48 weeks)	4.1 (3.6–4.8)	4.1 (3.5–4.7)	4.2 (3.8–5.0)

Data are median (interquartile range) or n (%) and assessed at baseline (day of randomization). Characteristics with significant difference (P value from Mann-Whitney or Fisher exact test < 0.05) between the study groups: HIV subtype (P = .033) and backbone regimen (P = .009). The remaining characteristics were balanced between the groups.

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; NA, not available; VL, viral load.

the plasma were below the 10th percentile. All dolutegravir concentrations in CSF exceeded the in vitro 50% inhibitory concentrations (IC 50) for wild-type HIV (0.2 ng/mL) [20].

Safety

Eight (7.9%) of 101 patients in the safety population developed serious adverse events (monotherapy 6 [8.8%] of 68; cART 2 [6.1%] of 33), none of which were deemed related to the study drug (Table 2). Adverse events related to the study drug occurred in 15 (14.9%) participants (monotherapy 9 [13.2%]; cART 6 [18.2%]). ART switch due to adverse events was less frequent in the monotherapy group (0%) than in the cART group (3 patients, 9.1%; P = .033). We noted no significant differences in change from baseline in renal function, proximal renal tubulopathy markers, total cholesterol, triglycerides, and low-density lipoprotein between groups at week 48 (Supplementary Figure 3, panels A and B; Supplementary Figure 4, panels A–D; Supplementary Figure 5, panels A–D).

DISCUSSION

Our early simplified randomized clinical trial shows noninferiority of dolutegravir monotherapy compared to cART in patients who initiated cART during primary HIV-1 infection and showed viral suppression for at least 48 weeks prior to switching to dolutegravir monotherapy. No virological failure occurred in the per-protocol population. This is in sharp contrast to previous randomized trials that revealed inferiority of

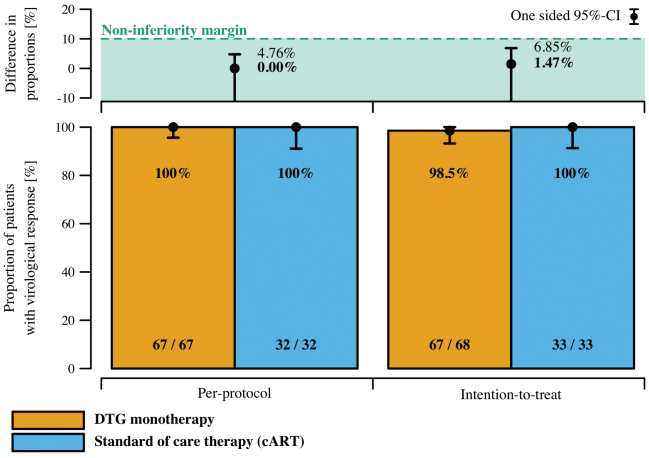

Figure 2. Virological response at week 48 defined as absence of virological failure in first 48 weeks for the per-protocol and intention-to-treat populations among the dolutegravir (DTG) monotherapy group (orange bars) and the standard-of-care combination antiretroviral therapy (cART) group (light blue bars). Virological failure is defined as 2 consecutive human immunodeficiency virus type 1 RNA >50 copies/mL in plasma. The proportion of patients with virological response in each group is depicted in the lower plot, while the upper plot summarizes the difference in proportions of patients with virological response between the study arms. The black symbols depict the proportions and the respective differences, and the error bars indicate the 95% exact confidence intervals (CIs). The light green shading represents the area of 95% CI upper bound for which the noninferiority is concluded. The CIs for the single proportions are the Clopper-Pearson (exact) CIs.

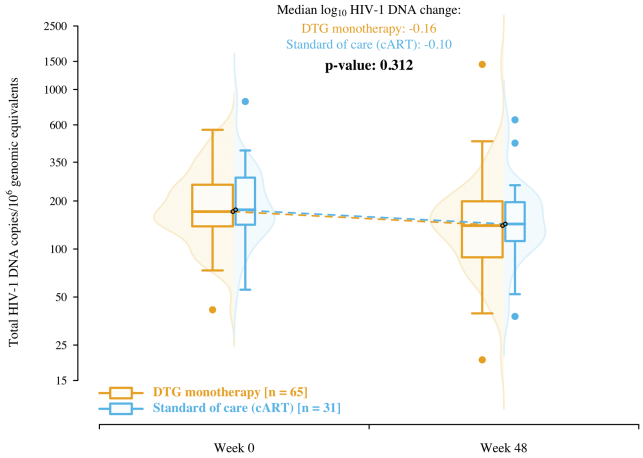

Figure 3. Total human immunodeficiency virus type 1 (HIV-1) DNA quantification from baseline compared to week 48 stratified by DTG monotherapy (orange) vs cART (blue). The shaded areas depict the distribution of the HIV-1 DNA values in both groups at baseline and at week 48. The dashed lines connect the medians of $\log_{10}$ HIV-1 DNA values at baseline and week 48. Abbreviations: cART, combination antiretroviral therapy; DTG, dolutegravir.

dolutegravir monotherapy compared to cART [6, 8, 9]; the virological failure rate was so high, that all studies were prematurely discontinued. Furthermore, emergence of drug resistance to currently licensed INSTIs occurred among patients failing on dolutegravir monotherapy [6, 8, 9]. Data from nonrandomized, partly retrospective clinical studies are less clear [21, 22]. Some studies show maintained viral suppression after switch from cART to dolutegravir monotherapy, others do not.

Notably, all prior dolutegravir monotherapy studies were conducted in patients who started their first cART during chronic HIV-1 infection. In contrast, we conducted our simplification study in patients who initiated cART during primary HIV-1 infection and were virologically suppressed for at least 48 weeks prior to entering the study. We chose this strategy because patients with early ART initiation have an approximately 10-fold lower latent HIV-1 reservoir [10, 11], less immune activation [23], and less viral diversity [12, 13] compared to patients who initiated cART during chronic infection. Our a priori hypothesis was that these properties would enable sustained virological suppression after simplification to dolutegravir monotherapy. With our novel approach to stratify patients for dolutegravir monotherapy according to their time of HIV-1 infection at the start of first cART, all patients maintained viral suppression. A potential explanation is that among patients with a small HIV-1 latent reservoir, the stochastic chance of activation of latently HIV-1–infected cells is less likely compared to patients with a large reservoir. Supporting this, the HIV-1 latent reservoir size predicted virological failures in the randomized controlled dolutegravir monotherapy trial conducted by Wijting el al [6, 24]. Moreover, the large variation in time to virological failure in this study suggests that stochastic reactivation could be the mechanism for failure [25]. In addition, a low nadir CD4 cell count and thus a surrogate for length of untreated HIV infection and a big reservoir size were predictive for virological failure in the MONCAY trial [9]. In addition, it has been shown that patients treated early with cART have less immune activation compared to those treated during chronic HIV-1 infection [23]. This may translate to a lower extent of activation of latently HIV-1–infected cells. Finally, patients who are treated early maintain a low level of viral diversity in blood as well as sanctuary sites, such as gut-associated tissue and the CNS [12, 26]; therefore, viral escape is less likely to occur.

To assess potential changes in the HIV-1 latent reservoir while on dolutegravir monotherapy, we measured total HIV-1 DNA levels in PBMCs from patients at baseline and at week 48 and found that there was a comparable slight decay in the total HIV DNA load in both groups. Our finding that the total HIV DNA load in the monotherapy group did not increase over time suggests that the HIV-1 latent reservoir was not replenished on dolutegravir monotherapy. Supporting this, the frequency of viral blips was very low in both treatment groups but even lower in the dolutegravir monotherapy group despite a much higher sampling frequency.

To investigate whether patients on dolutegravir monotherapy are at increased risk for CNS escape, that is, ongoing viral replication in the CNS in the presence of suppressed viremia in the plasma, we performed longitudinal lumbar punctures and

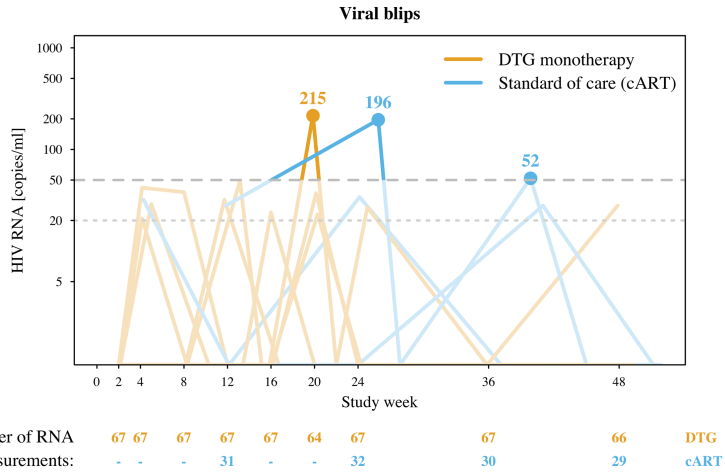

Figure 4. Viral blips stratified by dolutegravir (DTG) monotherapy vs standard-of-care combination antiretroviral therapy (cART). One patient in the DTG monotherapy group experienced a single blip at week 20, and 1 patient in the standard-of-care cART group had 2 blips. The light colors show the human immunodeficiency virus type 1 (HIV-1) RNA levels above the limit of detection (20 copies/mL; dotted light gray line), which were not classified as viral blips (>50 copies/mL; depicted by dashed gray line). Among the 13 patients with at least 1 HIV-1 RNA measurement above 20 copies/mL, four patients were from the cART group (3 participants with a single level >20 copies/mL and 1 with 3 HIV-1 RNA levels >20 copies/mL). In the DTG monotherapy group, one patient had 3 HIV-1 RNA levels >20 copies/mL, one patient had 2 HIV-1 RNA levels >20 copies/mL, and seven patients had a single HIV-1 RNA level above 20 copies/mL. The failing patient was excluded from this analysis.

measured the HIV-1 RNA in the CSF in a subset of patients at baseline and at week 48. In all CSF samples, HIV-1 RNA was not detected above the limit of quantification of 40 HIV-1 RNA copies/mL CSF at baseline (n = 37) and at week 48 (n = 12). We also measured dolutegravir drug levels in the CSF as a proxy for CNS penetration. In line with previous work [20], we found that in all patients on dolutegravir monotherapy or on dolutegravir-containing cART, the concentrations in CSF exceeded the in vitro IC 50 for wild-type HIV-1. This finding suggests that in our specific patient population, dolutegravir monotherapy is able to achieve therapeutic concentrations in the CNS and to prevent CNS escape at this sanctuary site.

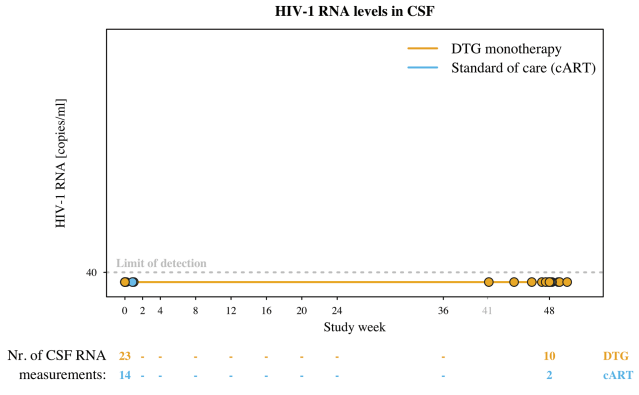

Figure 5. Human immunodeficiency virus type 1 (HIV-1) RNA measurements in the cerebrospinal fluid (CSF). Patients were asked to have a lumbar puncture performed at baseline and at week 48. The patient with virological failure at week 36 was the only patient who received an additional lumbar puncture at week 41. Orange and blue circles depict the single HIV-1 RNA measurements in CSF for the dolutegravir (DTG) monotherapy and standard-of-care combination antiretroviral therapy (cART) groups, respectively. The dotted gray line represents the detection limit.

The main goal of ART simplification is to reduce long-term toxicity associated with ART and to reduce costs. Indeed, almost all currently licensed antiretroviral drugs showed significant toxicity in post-marketing surveillance studies [27]. Thus, simplifying a patient to dolutegravir monotherapy could be a reasonable strategy to reduce long-term toxicity and daily pill counts in some patients. Although we did not find significant changes from baseline in lipid levels and proximal tubulopathy markers, it is possible that the follow-up time of 48 weeks was too short to detect clinically meaningful changes.

The strength of our study is that we tested a new and clear hypothesis for the first time: Do viral and immunological properties that result from early cART initiation translate into successful viral suppression after switch to dolutegravir monotherapy? We selected our patients based on a distinct clinical phenotype, and we combined our treatment intervention with several laboratory measurements to investigate the potential positive and negative impact of a dolutegravir monotherapy on toxicity markers, the HIV-1 reservoir, and potential CNS compartmentalization. A limitation of our study is that we were not able to recruit the targeted number (n = 138) of patients that was calculated for the targeted 80% power. Therefore, the study results rely on a small number of patients. The major reason for the low recruitment was the high frequency of patient visits we requested for safety reasons. Close HIV-1 RNA monitoring was performed in the dolutegravir monotherapy arm during the first 6 months to detect a potential virological failure as early as possible. Even though we enrolled fewer patients than

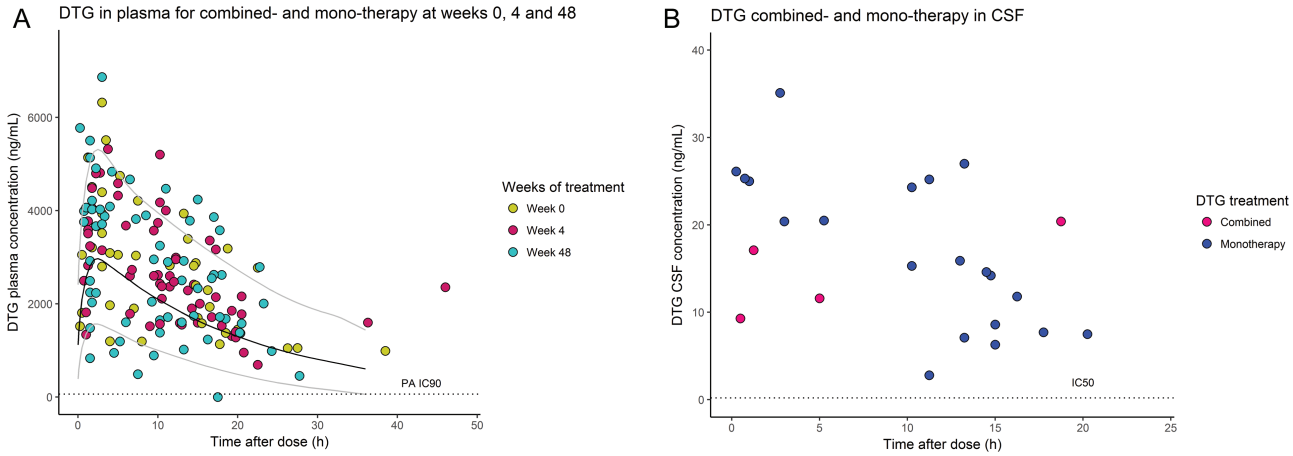

Figure 6. Dolutegravir (DTG) drug level measurements in plasma (*A*) and in CSF (*B*). *A*, Plasma DTG concentrations (yellow circles, week 0; red circles, week 4; green circles, week 48), with the median population predicted concentration (dark gray line) and the 10% and 90% prediction interval (light gray lines). The dashed black line represents the protein-adjusted 90% inhibitory concentration at 64 ng/mL. *B*, Cerebrospinal fluid DTG concentrations (blue circles, DTG monotherapy; purple circles, DTG combined with other antiretrovirals). The in vitro 50% inhibitory concentration of 0.2 ng/mL is represented by the dashed black line. Abbreviations: CSF, cerebrospinal fluid; PA IC90, protein-adjusted 90% inhibitory concentration.

Table 2. Adverse Events Among Study Participants

AE Among Study Participants	Overall	Monotherapy	Combination Antiretroviral Therapy	*P* Value
Number of patients[a]	87 (86.1)	61 (89.7)	26 (78.8)	.217
Study drug related	15 (14.9)	9 (13.2)	6 (18.2)	.557
Serious adverse event	8 (7.9)	6 (8.8)	2 (6.1)	1.000
Antiretroviral therapy switch due to AE	3 (3.0)	0 (0.0)	3 (9.1)	.033
Intensity				
Mild	86 (85.1)	60 (88.2)	26 (78.8)	.240
Moderate	18 (17.8)	10 (14.7)	8 (24.2)	.274
Severe	4 (4.0)	3 (4.4)	1 (3.0)	1.000
Laboratory AE	14 (13.9)	10 (14.7)	4 (12.1)	1.000
Laboratory AE, intensity				
Mild	13 (12.9)	10 (14.7)	3 (9.1)	.538
Moderate	1 (1.0)	0 (0.0)	1 (3.0)	.327
Sexually transmitted infection	30 (29.7)	23 (33.8)	7 (21.2)	.248
Common cold	21 (20.8)	16 (23.5)	5 (15.2)	.436
Other infection	14 (13.9)	13 (19.1)	1 (3.0)	.032
Headache	7 (6.9)	3 (4.4)	4 (12.1)	.212
Liver enzyme elevation	7 (6.9)	6 (8.8)	1 (3.0)	.422
Skin rash	7 (6.9)	4 (5.9)	3 (9.1)	.680
Arthralgia	6 (5.9)	4 (5.9)	2 (6.1)	1.000
Headache after lumbar puncture	7 (6.9)	4 (5.9)	3 (9.1)	.680
Creatinine elevation	5 (5.0)	2 (2.9)	3 (9.1)	.327
Sleeping disorder	5 (5.0)	4 (5.9)	1 (3.0)	1.000
Diarrhea	5 (5.0)	3 (4.4)	2 (6.1)	.661
Fatigue	4 (4.0)	2 (2.9)	2 (6.1)	.595
Back pain	4 (4.0)	4 (5.9)	0 (0.0)	.300
Commotio cerebri	4 (4.0)	3 (4.4)	1 (3.0)	1.000
Depression	3 (3.0)	2 (2.9)	1 (3.0)	1.000
Microhematuria	3 (3.0)	3 (4.4)	0 (0.0)	.549
Viremia	2 (2.0)	0 (0.0)	2 (6.1)	.105

Data are n (%).

Abbreviation: AE, adverse event.

[a]Number represents patients with at least 1 AE.

originally anticipated, noninferiority could be demonstrated. Since the power in noninferiority studies guarantees that the probability of showing noninferiority when the new treatment is indeed noninferior to the control is sufficiently high, the post study power is meaningless in case of significant results. Another possible limitation is the short follow-up period of 48 weeks. To address this limitation, we prolonged the study duration to 4 years at the time when the first studies reported a large number of patients failing on dolutegravir monotherapy. Finally, one potential limitation is that the frequent HIV-1 RNA measurements during the first 24 weeks might have increased adherence in the monotherapy group. However, these patients only came for short additional blood draw visits with the study nurse without counseling, and adherence, as measured by pill counts upon visits, did not differ between groups.

Our pilot study has potential implications for the management of HIV-1–infected patients. Our results suggest that success of simplification strategies using dolutegravir monotherapy is likely governed by early start of treatment with subsequent low latent HIV-1 reservoir size, low level of viral diversity, and low immune activation. It suggests that trials to evaluate simplification strategies should stratify between patients first treated during primary and chronic infection. This is of particular relevance because today all HIV-1–infected patients should be treated immediately regardless of their CD4 count [28]; thus, the fraction of patients treated early after infection most likely will increase. As our data show, these patients may be potentially overtreated for decades if patient population stratification is not performed in future simplification trials. Recent studies show that simplification with boosted protease inhibitors or dolutegravir each combined with lamivudine seem to work [29, 30], supporting the possibility that future ART could be personalized much more than it is today. One can even imagine that in the future, HIV-1 maintenance therapies will be started by measuring the size of the latent reservoir, for example, by proviral HIV-1 DNA or other future assays, and might be predictive of who can receive monotherapy. Therefore, more prospective controlled future simplification studies are needed that use stratification strategies according to the time of HIV infection and start of first cART guided by measurements of the latent reservoir. In addition, longer follow-up is important as for all prospective clinical cART trials because failure was observed after week 48 in several studies [6, 9].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. The study was designed by D. L. B. and H. F. G. Data acquisition was done by D. L. B., F. T., C. G., B. H., C. D., P. W. S., M. G., C. B., D. S., S. B., K. N., C. P., H. K., M. F., B. B., K. J. M., L. D., J. B., and H. F.G. Statistical analysis was performed by T. T. and R. D. K. H. F. G. supervised the study. D. L. B. wrote the first draft. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

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Data sharing agreement. The study protocol and individual participant data that underlie the results reported in this article will be available after deidentification following article publication to investigators whose proposed use of the data has been approved by an independent review committee to achieve aims in the approved proposal. Proposals should be directed to huldrych.guenthard@usz.ch to gain access. Data requestors will need to sign a data access agreement.

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