RESEARCH ARTICLE

Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: Systematic review and meta-analysis [version 1; referees: 3 approved]

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Abstract

Background: Dolutegravir-containing maintenance therapy is a promising simplification strategy for virologically suppressed HIV-infected individuals. However, most of the available data to inform this strategy come from small, uncontrolled studies. We estimated the proportion of HIV-infected patients experiencing virological failure (VF) and developing drug resistance on dolutegravir (DTG)-based maintenance therapy.

Methods: We searched Medline, Embase, Cochrane Central, Web of Science, and conference abstracts for studies assessing VF on DTG-based maintenance therapy. Studies including ≥5 adults with an undetectable viral load on antiretroviral therapy (ART) who switched to a DTG-based mono- or dual therapy were included. Pooled proportions of VF were estimated using random-intercept logistic meta-regression and acquired drug resistance mutations described for each strategy.

Results: Of 1719 studies considered, 21 met our selection criteria, including seven interventional and 14 observational studies. Eight studies including 251 patients assessed VF on DTG monotherapy and fourteen studies including 1670 participants VF on dual therapy. The participant's median age ranged from 43 to 63 years, their median nadir CD4 count from 90 to 399 cells/µl, and 27.6% were female. The proportion of participants experiencing VF on DTG-monotherapy was 3.6% (95% confidence interval [CI] 1.9-6.7) at 24 weeks and 8.9% (95% CI 4.7-16.2) at 48 weeks. Resistance mutations developed in seven (3.6%) participants on DTG-monotherapy. Among patients on dual therapy, ten (0.7%, 95% CI 0.4-1.3) experienced VF by 48 weeks and none developed resistance to DTG. In adjusted analyses, VF at 24 weeks was less likely on dual therapy than on monotherapy (adjusted odds ratio: 0.10, 95% CI 0.03-0.30).

Conclusions: Whereas VF is relatively common on DTG maintenance monotherapy, DTG-based dual therapy appears to be a promising simplification strategy for individuals with a suppressed HIV viral load on triple-ART.

Keywords

Dolutegravir, simplified therapy, HIV, meta-analysis

Open Peer Review

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Introduction

The concept of combination antiretroviral therapy (ART) for the treatment of HIV infection was established twenty years ago, when the results of the first studies evaluating protease inhibitor-based regimens were published[1]. In recent years, several strategies of treatment optimization and simplification gained interest, with the objectives of improving quality of life, minimizing ART-related toxicity and drug-drug interactions (DDI), as well as reducing health-related costs. So far, ART de-escalation from three to one (mono-) or two drugs (dual-) therapies has mainly been evaluated in virologically suppressed patients. The first simplified maintenance strategy studied included a boosted protease inhibitor (bPI), with the hope that the high genetic barrier to resistance would help achieve durable virological suppression. In a meta-analysis including ten studies, bPI monotherapy was found to be inferior to triple ART for the maintenance of viral suppression[2], but non-inferior with regards to loss of future treatment options[3]. In contrast, dual therapy with bPI and lamivudine (3TC) was found to be non-inferior to triple ART[4–6] and is now recognized as a valid switch strategy by current HIV treatment guidelines in selected situations[7]. However, bPI-based maintenance strategies are not widely applicable because of cost, toxicity and DDI.

Due to its interesting pharmacokinetic profile, good tolerability and high barrier to resistance, dolutegravir (DTG), a new integrase strand transfer inhibitor (InSTI), has attracted much interest for its use in simplified treatment regimens. While preliminary analyses of a Dutch DTG monotherapy simplification trial seemed encouraging at 24 weeks, rates of virological failures increased significantly by week 48, suggesting a suboptimal potency of this regimen[8]. On the other hand, several studies evaluating DTG-based dual therapy with either 3TC or rilpivirine (RPV), showed a high virological efficacy[9–12]. However, most reports were from small, observational cohort studies, with the exception of one DTG-RPV industry-sponsored randomized controlled trial (RCT)[11].

We performed a systematic review of the literature and a meta-analysis to provide precise estimates of the rate of virological failure (VF) and drug resistance in patients switched to a DTG-based maintenance mono- or dual therapy, and to clarify which drugs or combinations should be evaluated in further studies and implemented in clinical practice.

Methods

The protocol for this systematic review was written and registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42017070045)[13]. The reporting of the review followed the PRISMA guidelines[14] (Supplementary File 1).

Search strategy and selection criteria

We searched Medline, EMBASE, Cochrane Central and Web of Science, as well as abstracts of major HIV conferences (CROI, AIDS, HIV Glasgow, AFRAVIH, IAS and EACS between 2013 and 2017) on 4. January 2018 for studies assessing the proportion of individuals developing VF on DTG-based maintenance therapy. In Medline we combined free text words and medical subject headings (MESH) describing the study population and the outcome (Supplementary File 2). This search strategy was adapted for the other databases. We considered RCTs, single-arm clinical trials, cohort studies, and case-series that included at least five HIV-infected adults (≥18 years) on DTG-based simplified therapy. No language restrictions were applied. Studies had to report on virological outcomes of patients who switched to a DTG monotherapy or dual therapy after having an undetectable VL on triple ART. We excluded studies that only reported *in vitro* data and those selecting participants based on the outcome during DTG-based maintenance therapy. Two investigators (MB and GW) independently selected studies based on titles and abstracts, and, in a second step, based on the full text of potentially eligible articles. Discrepancies in study selection were resolved through discussions with a third investigator (AC).

Data extraction

The following data were extracted independently for each study by two reviewers (GW and MB), using a standardized spreadsheet: bibliographic details, study design, inclusion and exclusion criteria, definitions of outcomes, country, number of participants and their main demographic and clinical characteristics, including duration since HIV diagnosis, ART history, immunological status (CD4 cell count at switch and nadir) and virological parameters (HIV RNA peak and at baseline, HIV-DNA at baseline and changes during the study, VF as defined by the study, and the presence at drug resistance at switch). Again, discrepancies in data extracted were resolved through discussions with a third investigator (AC).

Assessment of risk of bias

A checklist for the assessment of risk of bias was designed to ensure data quality assessment for each study was included. The form for RCTs included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the randomized trials were assessed by two independent authors and classified as high, low or unclear risk of bias, as recommended by the Cochrane collaboration[15]. For observational studies it was not appropriate to use the ROBINS-I tool[16], as we only considered data from the group of patients on simplified, maintenance therapy. Thus, we assessed the population characteristics and missing outcome data for each study.

Data analysis

We described the study design as well as the demographic and clinical characteristics of the population from each study by type of maintenance therapy (DTG-based monotherapy or dual therapy). Pooled proportions of VF and treatment failure (VF or departure from simplified strategy due to toxicity, loss to follow-up, patient's or physician's decision), and 95% confidence intervals (CI) were estimated using random intercept logistic meta-regression. These analyses were performed separately at 24 weeks and 48 weeks after the switch from

triple ART to maintenance therapy. For all models, statistical evidence for heterogeneity between studies was assessed using the tau-squared statistics[17]. We evaluated the association between type of maintenance strategy and VF using random intercept logistic meta-regression (binomial-normal) models. All models were adjusted for potential confounders, including age (median or mean), sex (proportion of female participants) and study type (interventional or observational). Furthermore, the proportion of participants acquiring new drug resistance mutations was assessed for each treatment strategy and the mutations described in detail. Statistical analyses were conducted in STATA version 14.1 (StataCorp, Texas, USA) and R version 3.2.3 (R Core Team, Vienna, Austria).

Role of the funding source

The funder of the study had no role in the design, data collection, data analysis, data interpretation of the results or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study and participant characteristics

Of 1719 single studies identified, 63 remained potentially eligible after the screening of titles and abstracts. Of these, 21 studies, including four RCTs, three single-arm clinical trials and 14 observational studies met our inclusion criteria[8,11,12,18–35] (Figure 1). A description of the main study characteristics by type of maintenance strategy is given in Table 1. Eight studies (two from France, two from The Netherlands, one from Germany, one from Switzerland and two from Spain) including 251 patients assessed the switch to DTG monotherapy and 14 (five from Italy, four from France, three for Spain, one from US, and one multi-country study), including 1670 participants, the switch to DTG-based dual therapy. Dual therapy consisted of DTG + 3TC (seven studies) or RPV (four studies) or atazanavir (ATV, two studies) or darunavir (DRV, one study). Overall, 14 studies allowed the inclusion of patients with previous virological failure, including five monotherapy studies[18–20,22–24]. In one study, patients with previous InSTI failure were also included[12]. Nineteen studies assessed virological outcomes at six months of maintenance therapy, whereas ten of them additionally showed outcomes at one year[8,11,12,24,27,29–33,35]. Two studies assessed virological outcomes only at 48 weeks[25,27]. Median (or mean) age of participants included in the studies varied from 43 years[11] to 63 years[24] and 27.6% of them were female. 16 studies reported on the median nadir CD4 cell count, which ranged from 90 cells/µl[12] to 399 cells/µl[29].

Risk of bias

All RCTs were open-label non-inferiority trials[8,18,35], of which one was a single center trial[18] and three were multicenter trials[8,11,35].

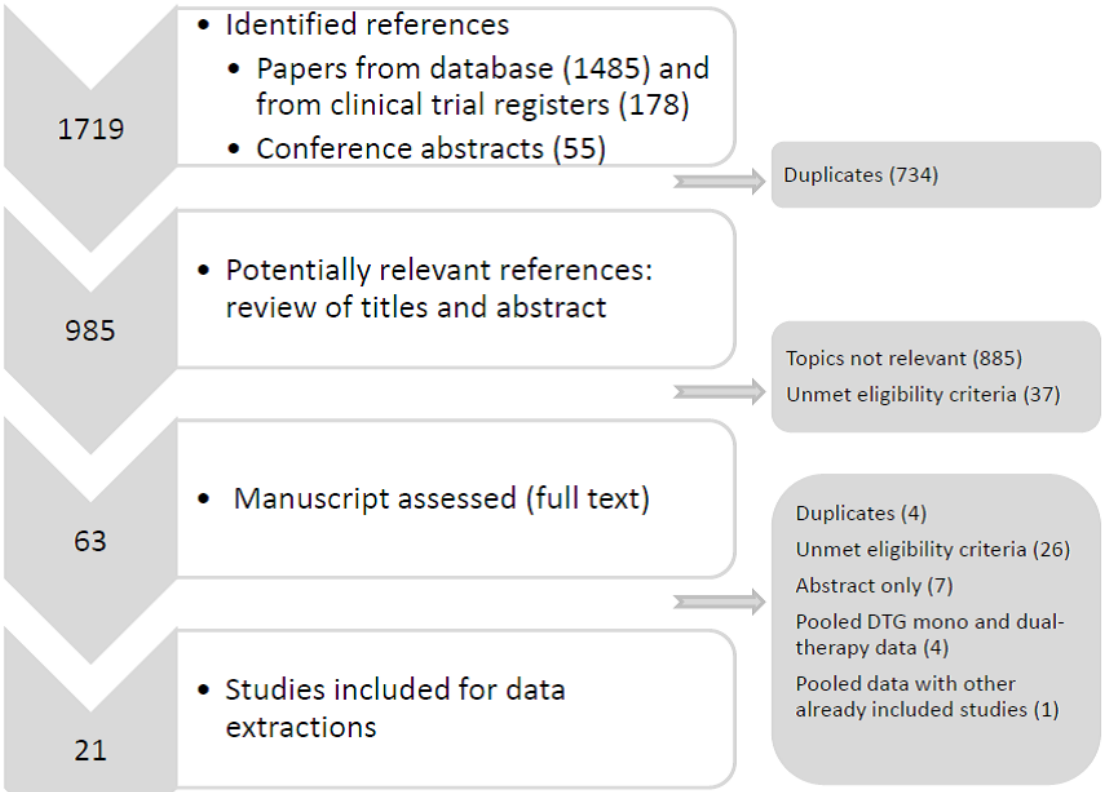

Figure 1. Flow chart of study selection process.

Table 1. Study characteristics, by treatment group.

Study	Country	Patients included (N)	Median/ mean age (years)	Female (%)	VF definition	Study type	Eligibility criteria					
							Previous VF allowed	Previous resistances allowed	Months of stable ART	Months with HIV VL<50	CD4 nadir (cells/ µl)	Other
DTG-Mono												
Katlama *et al. JAC 2016*	F	28	48	46.4	2× ≥ 50 cp/ml or 1× > 200 cp/ml	O	Yes	-	-	≥ 12	-	-
Wijting *et al. Lancet HIV*	NL	96	45.5	8.5	2× ≥ 200 cp/ml	I	No	No	-	≥ 6	>200	VL zenith <100.000
Gubavu *et al. JAC 2016*	F	21	47	38	2× ≥ 50 cp/ml	O	Yes	-	-	-	-	-
Oldenbüttel *et al. AVT 2016*	D	31	44.5	32	2× ≥ 20 cp/ml	O	Yes	Not to InSTI	-	≥ 6	-	no AIDS history
Rokx *et al. JAC 2016*	NL	5	63	0	2× ≥ 50 cp/ml	I	Yes	-	-	≥ 12	-	-
Rojas *et al. JAC 2016*	E	31	56	55	2× ≥ 37 cp/ml	O	Yes	-	-	-	-	-
Lecompte *et al. IAS 2017*	CH	8	44.5	28.5	1× ≥ 200cp/ml	I	No	No	≥ 24	-	-	-
Blanco *et al. JAC 2018*	E	31	47	10	2× ≥ 50 cp/ml or 1× > 1000 cp/ml	I	Yes	-	-	≥ 12	>200	-
DTG-3TC												
Borghetti *et al. JAC 2016*	I	36	53	19.4	2× ≥ 50 cp/ml	O	Yes	-	-		-	-
Maggiolo *et al. BMC ID 2017*	I	94	52	32.3	2× ≥ 50 cp/ml	O	Yes	Not to 3TC or InSTI	> 6	≥ 6	-	-
Joly *et al. CROI 2017*	F	104	45	14.4	2× ≥ 50 cp/ml	I	No	No	-	≥ 24	>200	no HIV encephalitis[£]
Reynes *et al. HIV Glasgow 2016*	F	27	59	25.9	2× ≥ 50 cp/ml	O	Yes	Not to InSTI	> 12	-	-	-
Blanco *et al. JAC 2018*	E	29	44	21		I	Yes	-	-	≥ 12	>200	-
Maggiolo *et al. EACS 2017*	I	203	52	24.6	-	O	Yes	No M184V	-	≥ 6	-	-
Taiwo *et al. CID 2017*	US	44	46	17	2× ≥ 50 cp/ml	I	No	No	≥ 12	≥ 12		

Study	Country	Patients included (N)	Median/ mean age (years)	Female (%)	VF definition	Study type	Eligibility criteria					
							Previous VF allowed	Previous resistances allowed	Months of stable ART	Months with HIV VL<50	CD4 nadir (cells/ µl)	Other
DTG-RPV												
Llibre *et al.* *Lancet 2018*	Multi-country	513	43	23	1× ≥ 50 cp/ml	I	No	-	> 6	≥ 12	-	-
Gantner *et al.* *HIV Med 2017*	F	116	55	44	2× ≥ 50 cp/ml or 1× ≥ 1,000 cp/ml	O	Yes	-	-	-	-	-
Bonijoly *et al.* *EACS 2017*	F	268	55	44	2× ≥ 50 cp/ml	O	Yes	-	-	≥ 6	-	On ART for ≥ 12 months
Revuelta *et al.* *Ann pharmacol 2018*	E	32	49	37	2× ≥ 50 cp/ml	O	Yes	Not to InSTI or RPV	-	-	-	-
DTG-ATV												
Riva *et al.* *HIV Glasgow 2016*	I	61	52.1	39	-	O	-	-	-	-	-	-
Castagna *et al.* *EACS 2017*	I	116	53	13	2× ≥ 50 cp/ml	O	-	-	-	≥ 12	-	-
DTG-DRV												
Navarro *et al.* *EACS 2017*	E	27	52	30	2× ≥ 50 cp/ml	O	Yes	Only to one ART class	-	≥ 6	-	-

Abbreviations: VF: virologic failure, ART: antiretroviral therapy, DTG: dolutegravir, 3TC: lamivudine, FTC: emtricitabine, RPV: rilpivirine, ATV: atazanavir, InSTI: integrase stand transfert inhibitor, F: France, NL: The Netherlands, D: Germany, E: Spain, CH: Switzerland, I: Italy, USA: United States of America, O: observational study; I: interventional study

£: no abnormal standard biological parameter

They reported adequate generation of random allocation sequences and allocation concealment. Three single-arm trials were included, of which two included less than 10 patients[21,24,29]. All interventional studies adequately addressed incomplete outcome data: proportions of drop-outs were low and outcome data were missing for less than 20% of participants in all studies. Five of seven trials reported on virological outcomes at both time-points of interest for this study (24 and 48 weeks)[8,11,24,29,35]. There was no evidence of selective reporting in any of the studies. In each of the 14 observational studies included in this review, the main demographic and clinical characteristics of the study populations were similar and patients were followed for 24 weeks in most studies. Among the observational studies, the majority did not report detailed inclusion and exclusion criteria. Five observational studies reported virological outcomes at both time-points[12,30–33]. Amplification for drug resistance testing was successful for 19 of the 27 (70%) patients with VF. Finally, patient retention was over 90% in all 14 cohort studies.

Virological and treatment failure

The pooled estimate of the proportion of participants who experienced a VF on DTG-based monotherapy was 3.6% (95% CI 1.9-6.7) at 24 weeks and 8.9% (95% CI 4.7-16.2) at 48 weeks (Figure 2). The high proportion of treatment failures among

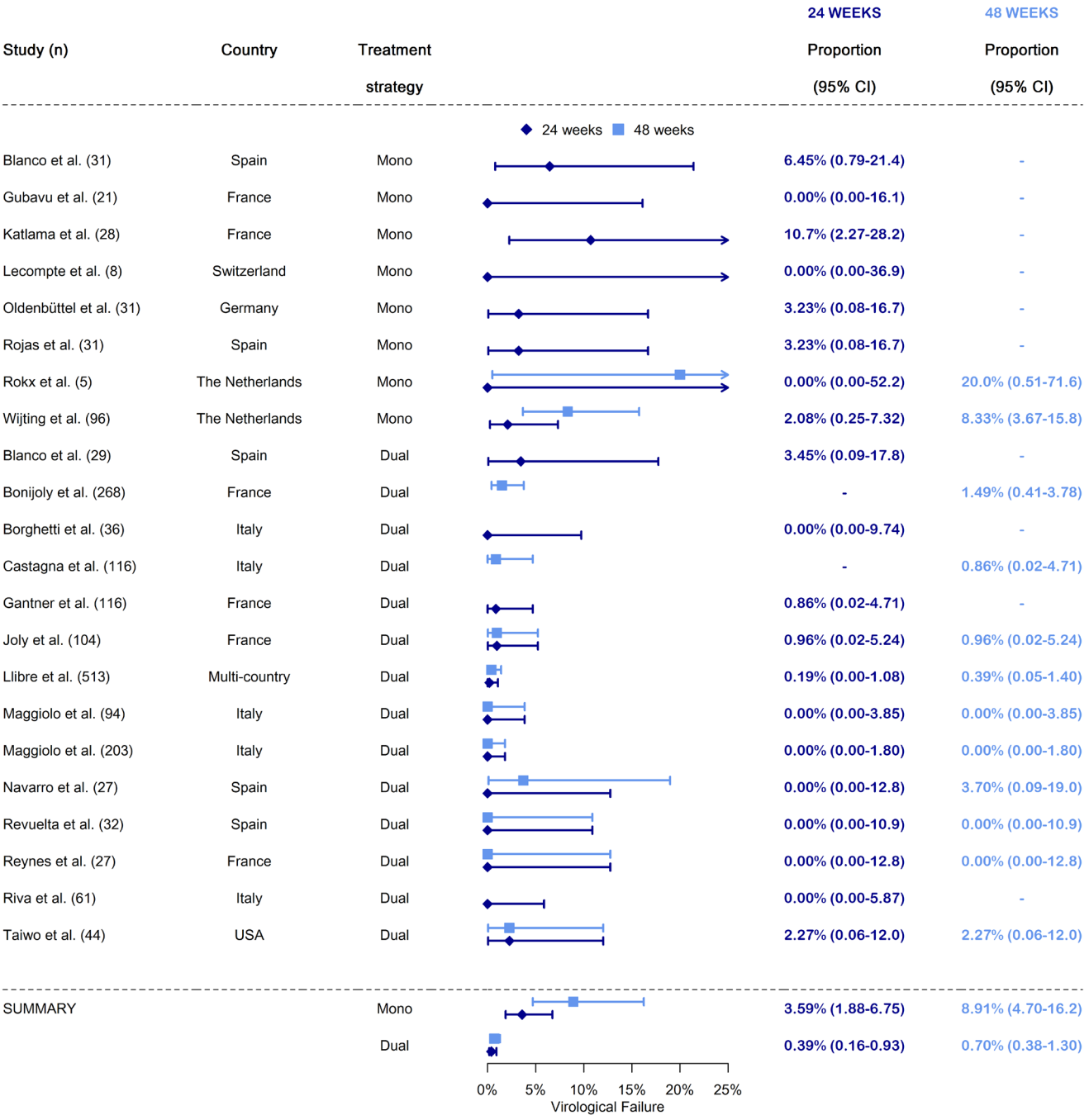

Figure 2. Meta-analysis of virological failure among patients on single or dual DTG-based simplification therapy.

patients on monotherapy at 48 weeks was driven by the two studies from the Netherlands, which observed between 8 and 20% of VF[8,24]. Among patients on dual therapy, an estimated 0.4% (95% CI 0.2-0.9) experienced a VF at 24 weeks and 0.7% (95% CI 0.4-1.3) at 48 weeks. Independently of the combination used (DTG/3TC, DTG/RPV, DTG/ATV or DTG/DRV), 11 of 14 studies evaluating the effectiveness of dual therapy had less than 1% of patients developing VF. Compared to patients on monotherapy, those on dual therapy were less likely to experience VF by 24 weeks (odds ratio [OR] 0.10, 95% CI 0.03-0.32, p<0.001) and 48 weeks (OR 0.07, 95% CI 0.03-0.18, p<0.001). In analyses adjusted for study type (interventional or observational), age (median or mean) and sex (proportion of female participants), the OR for VF at 24 weeks and 48 weeks were very similar to the unadjusted estimates (aOR 0.10, 95% CI 0.03-0.30 for 24 weeks and aOR 0.06, 95% CI 0.01-0.30 for 48 weeks, respectively). The only variable that contributed to explaining the between-study heterogeneity in both the 24 and 48-week analyses was treatment strategy. When including this variable, the tau-squared were reduced from 1.17 (95% CI 0.33-2.19) to 0.00 (95% CI 0.00-1.11) in the 24 week analysis and from 1.37 (95% CI 0.54-2.15) to 0.00 (95% CI 0.00-1.00) in the 48 week analysis. The inclusion of other variables did not impact the estimates of tau-squared.

Treatment failure occurred in 5.2% (2.0–12.9) of patients at 24 weeks and 12.3% (4.5–29.4) at 48 weeks on DTG-monotherapy, whereas this outcome was observed in 2.8% (1.4–5.7) of patients at 24 weeks and 6.5% (4.3–9.6) at 48 weeks on DTG-based dual therapy. At 24 weeks, patients on dual therapy tended to be less likely to experience treatment failure compared to those on monotherapy (aOR 0.52, 95% CI 0.15-1.85). Due to multi-collinearity in the model, we were not able to report on multivariable analyses comparing treatment failure between mono and dual therapy at 48 weeks.

Drug resistance

Acquired resistance mutations to InSTI developed in 9/251 (3.6%) participants on DTG-based monotherapy, which corresponded to 56% of the cases of VF (Table 2). Three individuals

Table 2. Virological outcomes and drug resistance, by study.

Study	Follow-up (weeks)	N° patients	N° treatment failures (%)		N° virological failures (%)		N° amplified	N° patients with resistance	Resistance patterns (one line per patient)*
			24 weeks	48 weeks	24 weeks	48 weeks			
DTG-Mono									
Katlama *et al.*	24	28	4 (14.3)	-	3 (10.7)	-	3	**3**	**E138K,G140A, Q148R E92Q N155H**
Wijting *et al.*	48	96	-	11 (11.5)	2 (2.1)	8 (8.3)	6	**3**	**S230R R263K N155H**
Gubavu *et al.*	24	21	0	-	0	-	-	-	
Oldenbüttel *et al.*	24	31	2 (6.5)	-	1 (3.2)	-	1	**1**	**Q148H, G140S**
Rokx *et al.*	48	5	0	1 (20)	0	1 (20.0)	1	0	
Rojas *et al.*	24	31	1 (3.2)	-	1 (3.2)	-	1	0	118R**
Lecompte *et al.*	24	8	1 (12.5)	-	0	-	-	-	
Blanco *et al.*	24	31	2 (6.5)	-	2 (6.4)	-	2	**2**	E138A, S147G, N155H, Q148R 138K, 155H, 140S
DTG-3TC									
Borghetti *et al.*	24	36	3 (8.3)	-	0	-	-	-	
Maggiolo *et al.*	48	94	0	3 (3.2)	0	0	-	-	
Joly *et al.*	48	104	1 (1.0)	3 (2.9)	1 (1.0)	1 (1.0)	0	-	
Reynes *et al.*	48	27	3 (11.1)	3 (11.1)	0	0	-	-	
Blanco *et al.*	24	29	1 (3.5)	-	1 (3.4)	-	1	0	K70E***, K219E***, G190R$, M230I$
Maggiolo *et al.*	48	203	0	12 (6.0)	0	0	-	-	
Taiwo *et al.*	48	44	1 (2.3)	3 (6.9)	1	1	1	0	

Study	Follow-up (weeks)	N° patients	N° treatment failures (%)		N° virological failures (%)		N° amplified	N° patients with resistance	Resistance patterns (one line per patient)*
			24 weeks	48 weeks	24 weeks	48 weeks			
DTG-RPV									
Llibre *et al.*	48	513	-	27 (5.3)	1 (0.2)	2 (0.4)	2	1	K101K/E
Gantner *et al.*	24	116	11 (9.5)	-	1 (0.9)	-	0	-	
Bonijoly *et al.*	24	268	-	51 (19.0)	-	4 (1.5)	-	-	
Revuelta *et al.*	48	32	-	2 (6.5)	0	0	-	-	
DTG-ATV									
Riva *et al.*	24	61	3 (4.9)	-	0	-	-	-	
Castagna *et al.*	48	116	5 (4.3)	6 (5.2)	-	1 (0.9)	-	-	
DTG-DRV									
Navarro *et al.*	48	27	-	2 (7.4)	0	1 (3.7)	1	0	

*bold: InSTI resistance

**in 7% of integrated DNA in PBMC

*** in ≤1.5% of integrated DNA in PBMC

£ in integrated DNA in PBMC

developed the Q148R or Q148H mutation in combination with other resistance mutations, conferring high-level resistance to DTG[20,22]. These three patients did not have a history of previous VF and had a suppressed HIV viral load for several years before switching to DTG-monotherapy. No InSTI resistance mutations developed in patients on dual therapy. Of 962 patients on RPV/DTG, only one developed a major drug resistance mutation to non-nucleoside reverse transcriptase inhibitors (K101E). No resistance was observed in plasma among 237 individuals on DTG/3TC.

Dataset 1. Dolutegravir meta-analysis summary data

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This table shows summary measures, including the number of virological and treatment failures in each study.

Discussion

We performed a comprehensive systematic review of studies that reported on VF among patients switched to DTG-based maintenance therapy. Our meta-analysis shows that DTG-based dual therapy is successful in sustaining virological control in ART-experienced HIV-infected patients: only 12 of 1670 (0.7%) experienced a VF and none of them developed resistance mutations to DTG. On the contrary, 16 of 251 (6.4%) individuals switched to DTG monotherapy had a VF, of which more than one-half developed resistance to DTG. Although the proportion of patients experiencing a confirmed viral rebound on DTG-monotherapy does not seem to be higher than in patients on PI-monotherapy, the risk of losing future treatment options is higher with DTG-monotherapy[3]. Overall, our findings suggest that DTG-based monotherapy is not an appropriate simplification strategy and that further studies are urgently needed to confirm the long-term efficacy of DTG-based dual therapy.

DTG-based dual therapy is a promising simplification strategy, especially when combined with 3TC or emtricitabine (FTC, both compounds referred to as XTC), as the likelihood of developing toxicity events and DDI on such regimens is very low. No drug resistance mutations to DTG developed among more than 1600 patients on dual therapy followed for 24 to 48 weeks and only one had a resistance mutation to another drug class. Although based on very few patients, the results seemed to be independent of previous virological failures. For instance, no virological failures were noted among patients on DTG/3TC despite the presence of a 184V mutation at the time of simplification in several studies. The impact of the latter mutation on viral fitness has been extensively described and could also potentially explain the improved treatment outcomes in these patients compared to those switched to DTG-monotherapy without any previous failures. Interestingly, similar observations were made for bPI-based regimens, for which efficacy was improved when 3TC was added, despite the presence of the 184V mutation[36]. Although the proportion of patients experiencing a confirmed viral rebound on DTG-monotherapy does not seem to be higher than in patients on PI-monotherapy, their chances of losing future treatment options is higher than reported in most PI-monotherapy trials

We also report on estimates of treatment failure, which includes other reasons for treatment interruptions, such as toxicity or loss to follow-up. In our meta-analysis, the proportion of patients experiencing this combined outcome was more than twice as high among patients on monotherapy compared to those on DTG-based dual therapy. Although this outcome is important in evaluating the clinical efficacy of a novel ART strategy,

our capacity to analyze this outcome in detail was limited by the missing information on the specific reasons for treatment interruptions in many studies and by the small number of events, especially at 48 weeks of therapy.

Of all simplification strategies evaluated to date, the DTG/XTC combination could be the one most readily accessible for patients in low- and middle-income countries: both DTG and XTC are available and prequalified by stringent regulatory authorities in generic formulations. In order to be widely implemented, the efficacy of this dual combination should first be evaluated in large studies among different patient populations. The results from the studies included in our meta-analysis are mainly based on selected populations of HIV-infected individuals from European cohorts, and are not generalizable. Furthermore, long-term data are needed, as most treatment failures occurred after the first 24 weeks in several monotherapy studies. Recently, results from the only study which assessed 96-week outcomes with this regimen to date were reported: among 27 ART-experienced individuals with previous VF, DTG/3TC was 100% efficacious virologically[12]. However, despite these encouraging results, data from larger studies are needed. In addition, more data on the activity of DTG-based simplified regimens in compartments other than blood are needed. Letendre *et al*. showed that DTG achieved therapeutic concentrations in the central nervous system (CNS), with a CNS penetration effectiveness score of four[37]. However, these results were based on a very small sample of patients and data from individuals on simplified, DTG-based therapies are lacking.

As a wealth of data on the efficacy of DTG-maintenance strategies from small studies are being disseminated at a fast pace, this systematic review is the first analysis to provide comparative estimates of virological failure between DTG-based monotherapy and dual therapy. More than 1700 studies were screened, including abstracts from all important HIV conferences in the past years. As our meta-analysis included studies with diverse study designs and populations, it could be argued that the comparison of studies with such differences might be problematic. However, the estimates of VF were very similar across studies, especially in the DTG-based dual therapy arm. This finding highlights the potency of this combination, even in the presence of previous drug resistance mutations or multiple co-morbidities. Unfortunately, only studies including low numbers of patients reported outcomes from individuals on DTG-monotherapy, and data on dual therapy was dominated by one large study that assessed the efficacy of the DTG/RPV combination. As a consequence, the comparison of DTG-monotherapy vs. DTG/XTC, which would have been the most interesting one, was not possible. Furthermore, the lack of availability of individual data from the different studies precluded the analysis of risk factors of VF in the different simplification regimens. As most studies were observational, it is possible that the investigators mainly included patients with good adherence, which may have limited the generalizability of their findings. Finally, our results might have slightly under-estimated the proportion of patients with VF as individuals who were lost to follow-up might have experienced this outcome without them being accounted for. However, our treatment failure estimates showed that even when other reasons of treatment failure were considered, DTG-based dual therapy was superior to monotherapy.

In summary, DTG-based dual maintenance therapy seems to be a promising simplification strategy with high virological efficacy and low potential for DDI and toxicity. Such a treatment regimen could be an interesting alternative to classical triple-ART in selected patients. Furthermore, dual therapy might be a cost-effective global ART strategy[38]. A number of large prospective studies evaluating the efficacy of DTG-based dual therapy are under way and will inform its potential implementation at a large scale. In addition to the studies on maintenance therapy[39,40], clinical trials are also assessing the efficacy of DTG/XTC in treatment-naïve patients[41]. Furthermore, it will be critical to evaluate the efficacy of DTG-XTC dual therapy in specific sub-groups such as pregnant and breast-feeding women, adolescents, patients with previous failure to standard triple regimens and harboring the M184V resistance mutation, as well as in patients with HIV associated neurocognitive disorder and tuberculosis coinfection.

Data availability

F1000Research: Dataset 1. Dolutegravir meta-analysis summary data., 10.5256/f1000research.15995.d215724[42]

Grant information

This study was supported by the Swiss National Science Foundation (Ambizione-PROSPER fellowship PZ00P3_154730 to GW, grant 32FP30-174281 to ME, and grant 33IC30_166819 to AC).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material

Supplementary File 1: Completed PRISMA checklist.

Click here to access the data.

Supplementary File 2: Search strategy for Medline.

Click here to access the data.

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http://www.doi.org/10.5256/f1000research.15995.d215724

Open Peer Review

Current Referee Status: ✔ ✔ ✔

Version 1

Referee Report 10 September 2018

doi:10.5256/f1000research.17470.r37756

✔ **Omar Sued**
Fundación Huésped, Buenos Aires, Argentina

The topic is extremely important, the conclusion is very relevant for informing the clinical practice and the timing is perfect.
Please see below some comments to improve this excellent systematic review

- Note that reference 9 is for naive patients, and not for switching.
- REPRODUCIBILITY: Risk of bias checklist is not available. It could be good idea to include as supplementary material a sample of the checklist of assessment of bias.
- The number of reviewed studies is 21, but the authors reported 8 for monotherapy and 14 for dual therapy without clarifying that some are focused on both strategies.
- Similarly, in figure 2, the name of the author is followed by the (n) of participants. This makes the reader think this is the reference. Please consider to add the reference number in this place, and an additional column for "n"
- Regarding the phrase "These three patients did not have a history of previous VF and had a suppressed HIV viral load for several years before switching to DTG-monotherapy". Please comment if patients experiencing INSTI resistance in monotherapy were previously exposed to INSTI.
- Please review Table 2, because some INSTI mutations are not in bold, and the $ symbol is not explained in notes
- In discussion you mention "For instance, no virological failures were noted among patients on DTG/3TC despite the presence of a 184V mutation at the time of simplification in several studies." but you are not showing this result. Given the potential clinical importance of this issue, consider show how many participants had this mutation and show the outcomes.
- In the discussion, these phrases look similar:

1. First Paragraph: "Although the proportion of patients experiencing a confirmed viral rebound on DTG-monotherapy does not seem to be higher than in patients on PI-monotherapy, the risk of losing future treatment options is higher with DTG-monotherapy"
2. Second Paragraph "Although the proportion of patients experiencing a confirmed viral rebound on DTG-monotherapy does not seem to be higher than in patients on PI-monotherapy, their chances of losing future treatment options is higher than reported in most PI-monotherapy trials"

- Why to mention DTG-XTC if no study was presented with FTC?. I would suggest to stick to the presented data, therefore to discuss about 3TC.
- The phrase "In addition to the studies on maintenance therapy[39,40], clinical trials are also assessing the efficacy of DTG/XTC in treatment-naïve patients" should be updated based on the results of GEMINI1&2.

- It could be good to try to explain the higher rate of failure in those three trials in dual therapy (Blanco, and Navarro). Please check the failure rate in figure 2 for Taiwo (44 patients with failure 2.7%).

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: I received an Investigator Research Grants from ViiV and travel grants from Richmond.

Referee Expertise: HIV clinical trials

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 10 September 2018

doi:10.5256/f1000research.17470.r37757

Laurent Hocqueloux
Orleans Regional Hospital Centre (CHR Orléans), Orléans, France

Wandeler and colleagues provide here an excellent and comprehensive review on DTG-based maintenance therapy, even though this review will lack the latest communications on the topic (at IAS 2018). Nevertheless, the conclusions they make are in accordance with what is currently admitted by experts in the field and worldwide guidelines: DTG monotherapy lead to an unacceptable virologic failure (VF) rate (because of >50% of emerging mutations to the class) whereas dual therapy has an excellent efficacy and no VF with mutations to the class.

I only have minor comments or questions:
Results:

- (page 4) Can the authors provide any data on the impact of CD4 nadir on VF during monotherapy (as described by Wijting in the DOMONO trial)?
- (page 8) Authors should give more explicit conclusion on this paragraph “The only variable that contributed to explaining the between-study heterogeneity in both the 24 and 48-week analyses was treatment strategy. When including this variable, the tau-squared were reduced from 1.17 (95% CI 0.33-2.19) to 0.00 (95% CI 0.00-1.11) in the 24 week analysis and from 1.37 (95% CI 0.54-2.15) to 0.00 (95% CI 0.00-1.00) in the 48 week analysis. The inclusion of other variables did not impact the estimates of tau-squared.”

Discussion:

- (page 9) Please provide some references (at least one) for the impact of M184V on viral fitness (this one is of interest for DTG-based regimen: doi: 10.1097/QAD.0000000000001191)
- (page 9) I think authors should provide some data on VF (%, emerging mutations) during switch from a triple therapy to another one (in order to have an “historical comparator” for dual therapy)
- (page 10, “In addition, more data on the activity of DTG-based simplified regimens in compartments other than blood are needed.”) There are some references for mono- or dual-therapy in the genital tract (Hocqueloux et al.[1] and Gianella et al.[2])and CNS (Doco Lecompte et al.[3])
- (page 10) Authors should cite recent reports (all communicated at the IAS 2018 in Amsterdam) confirming their conclusions, even though they cannot include them in the analyses: two randomized-controlled clinical trials on DTG monotherapy (Braun et al.[4] and Hocqueloux et al.[5]), the extended follow-up of the SWORD trials at week 100 (Aboud et al.[6]) and results of the GEMINI trials (Cahn et al.[7]).

References:

- (references 25 and 28) I think two references (Gantner and Bonijoly) are duplicates (as they are based on the analyze of the same database; Bonijoly et al. have included more patients / with longer duration of follow-up than Gantner).

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Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I have received personal fees from Abbvie, Gilead, Janssen, MSD and ViiV Healthcare for advisory boards and travels.

Referee Expertise: Monotherapy and dual therapy, HIV reservoirs, primary-infection, post-treatment control.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 03 September 2018

doi:10.5256/f1000research.17470.r37755

Esteban Martinez
Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

This paper compared the efficacy of dolutegravir-based monotherapy vs dual therapy using the methodology of systematic review and meta-analysis. The topic is of great interest as many different studies with these simplication strategies have been done. Although dolutegravir monotherapy is not recommended at present due to the risk of virological failure with development of resistance mutations and dolutegravir dual therapy seems a promising strategy with recent evidence from large clinical trials, this systematic review and meta-analysis is timely because there are almost no direct comparisons between dolutegravir-based monotherapy vs dual therapy. The design and the methods (including PRISMA reporting) are adequate, as they are the interpretation of results. It is interesting that not only

monotherapy was inferior to dual therapy but the difference resulted highly increased from 24 weeks to 48 weeks of follow-up, thus indicating that the risk of failure with the monotherapy strategy may greatly increase after the initial 24 weeks of follow-up. This is remarkable as many exploratory studies had 24-week results only.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I have received grants and honoraria for lectures or advisory boards from Gilead, Janssen, MSD, and ViiV.

Referee Expertise: Antiretroviral therapy strategies, complications of HIV infection and its therapy

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.