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Clinical Impact of Virological Failure and Resistance Analysis Definitions used in Pivotal Clinical Trials of Initial Antiretroviral Treatment: A Systematic Review

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Abstract

There are no standardized criteria to characterize confirmed protocol-defined virological failure (PDVF) nor the inclusion criteria for the resistance analysis population (RAP) in Phase III randomized clinical trials (RCTs) of initial antiretroviral therapy (ART). We assessed the clinical impact of mismatching between virological non-response (HIV-1 RNA ≥50 copies/mL), confirmed PDVF (48 weeks), and RAP definition in studies with the newest first-line ART. A systematic review of all Phase III RCTs was performed, including preferred once-daily ART (EACS European AIDS guidelines) or recently approved by the US Food and Drug Administration. We identified 16 treatment arms (14 RCTs) with 6175 participants treated with dolutegravir, bictegravir, elvitegravir/cobicistat, raltegravir, darunavir/cobicistat, rilpivirine, or doravirine. Plasma HIV-1 RNA thresholds for PDVF or RAP ranged from 40 to 50, 200, 400, and 500 copies/mL. This led to discrepancies between trials regarding the participants defined as virological non-responders, PDVF, or included in RAP. Overall, 85/296 (29%) patients with PDVF were not genotyped. There was a linear correlation between the threshold of HIV RNA chosen to perform genotyping and rates of participants with PDVF but not genotyped. Only eight treatment arms genotyped all participants with PDVF. Most of the remaining eight arms genotyped roughly < 50% of those with PDVF. In summary, the absence of standardized definitions of VF and criteria for resistance testing in pivotal Phase III RCTs of the first-line ART leads to the possibility of underreporting of resistance mutations when genotypes are only performed at higher viral load cutoffs. Stringent homogeneous criteria should be defined to ensure that all participants with PDVF (e.g., confirmed HIV RNA ≥ 50 copies/mL and the second > 200 copies/mL) undergo genotyping. **(AIDS Rev. 2018;20:158-170)**

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Key words

Clinical trials. Virological failure. HIV resistance. Initial antiretroviral treatment. HIV genotype.

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Introduction

Large Phase III randomized clinical trials (RCTs) required for antiretroviral drug approval by regulatory agencies have standardized definitions for their primary endpoints with regard to treatment failure and virological success. However, there is no uniformity in the definition of virological failure (VF) or HIV-1 RNA threshold chosen for resistance analysis performance. There are no rules governing which samples (first or confirmatory) are sent for HIV resistance assessment[1]. While drug regulatory agencies thoroughly review the study protocols, this variability between protocols is allowed. These differences in the study defined "resistance analysis population" (RAP) among trials result in dissimilar rates of participants with VF whose samples are submitted for resistance evaluation. Furthermore, some samples cannot be amplified, and therefore, results cannot be interpreted.

When evaluating the virological results of pivotal RCTs, clinicians are mostly influenced by the rates of participants with confirmed drug resistance mutations (DRMs) isolated at failure. However, those participants having experienced VF to regimens with low barrier against resistance development and with no resistance results available will nevertheless have subsequently some clinical implications that could be missed with this straightforward interpretation. A history record of this failure might grant a restriction to access to some future simplification antiretroviral regimens or dosing due to suspected resistance or cross-resistance in the drug class (i.e., integrase inhibitors).

In this review, we aimed to assess the clinical impact of mismatching between virological non-response, VF, and RAP definition in RCTs with the newest once-daily first-line antiretroviral regimens. Our aim is to identify the rates of HIV-infected participants with confirmed HIV-1 RNA ≥ 50 copies/mL that finally do not have a valid genotype at a standardized week 48 analysis, and therefore, there is no certainty about their lack of resistance selection during VF.

Methods

We completed this systematic review using PRISMA guidelines[2]. We undertook a systematic review of VF outcomes at week 48 in all Phase III, non-inferiority RCTs including treatment-naïve HIV-1-infected adults receiving the once-daily triple-drug regimens considered preferred in European guidelines[3] or recently approved by the US Food and Drug Administration (FDA). Regimens consisted of a dual coformulated nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone, combined in a once-daily regimen with either a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (bPI), or an integrase strand transfer inhibitor (INSTI). When data were available with coformulations including tenofovir alafenamide and tenofovir disoproxil fumarate with the same third drug (i.e., darunavir or elvitegravir), only tenofovir alafenamide arms were considered. European, Spanish, International, and US guidelines recommend tenofovir alafenamide as a first choice due to favorable bone density and kidney safety[3-6].

In each RCT, we collected the rates of participants with HIV-1 RNA ≥ 50 copies/mL in the snapshot analysis done at 48 weeks, the protocol-defined VF (PDVF) criteria and rates, the HIV-1 RNA criteria defined for resistance testing, the samples used to test for resistance (first one above a defined viral load threshold or the second and confirmatory sample) at the time of VF, the rates of participants genotyped for resistance but with non-valid results, and the emergent DRM against the third drug or the NRTI backbone (Tables 1 and 2). Furthermore, we specifically analyzed the rates of participants with confirmed VF and an HIV-1 RNA > 200 copies/mL even if this was not the predefined limit in the trial. This threshold has shown the highest degree of agreement between three US FDA-approved HIV-1 RNA assay platforms while minimizing differences observed between assays and has important implications for the definition of VF in clinical trials, guidelines, and clinical practice[6,7].

Data shown in tables 1-3 were retrieved from data published or presented in International conferences identified through a systematic review, including the main study data and all the secondary presentations/publications. When data were incomplete or unavailable, they were obtained from the clinical trials investigators on request.

Virological non-response is defined as the percentage of participants with VL ≥ 50 copies/mL at 48 weeks, using an intention-to-treat analysis with either the US FDA-defined snapshot algorithm or the time-to-loss of virological response according to each study.

We performed a Cochran–Armitage test to assess whether the association between the HIV-RNA threshold chosen to perform a genotype resistance test in every study and the rate of participants with PDVF that was not submitted for genotyping followed a trend (dose–response effect).

Results

We identified 14 clinical trials that comprised 16 treatment arms and recruited 6175 participants. No studies were excluded from the study. The main trial characteristics and outcomes are shown in table 3. We assessed 10 arms with the INSTIs bictegravir (*n* = 2), dolutegravir (*n* = 6), elvitegravir/cobicistat (*n* = 1), or raltegravir (*n* = 1), 5 arms with the NNRTIs rilpivirine (*n* = 3) or doravirine (*n* = 2), and one arm with the bPI darunavir/cobicistat.

PDVF criteria were not homogeneous among the studies (Table 1). The threshold used in plasma HIV-1 RNA for the definition of VF or the composition of the RAP ranged from 40 to 50, 200, 400, and even 500 copies/mL. All participants with virological non-response at 48 weeks were considered PDVF in SPRING-2[8,9], GS-US-380-1489[10,11] and 1490[12,13], GS-US-292-0104/0111[14-16] and STaR[17-20]. However, the remaining studies showed a discrepancy between virological non-response - a parameter that has a standardized definition - and PDVF compositions. The percentages of participants with virological non-response included in the PDVF population were 85.7% (18/21) in SINGLE[21,22], 13.3% (2/15) in FLAMINGO[23], 37.5% (6/16) in ARIA[24,25], 50% (8/16) in AMBER[26], 56.4% (22/39) in DRIVE-AHEAD[27], and 44.2% (19/43) in DRIVE-FORWARD[28].

Therefore, FLAMINGO showed the lowest rate of participants with virological non-response meeting PDVF criteria. One dolutegravir study (ARIA) did not have a definition for VF, but only for confirmed virological withdrawal. Conversely, three studies (ONCEMRK[29], ECHO[30-32], and THRIVE[31-33]) reported a higher number of participants with PDVF than with virological non-response.

In addition, not all participants classified as PDVF in the studies were included in the RAP population and were subsequently genotyped.

The definitions used for VF (PDVF) were not infrequently different than those chosen for the inclusion in the RAP, and therefore, there were a variable number of participants with confirmed VF that was not subsequently genotyped (Table 2 and Fig. 1). In one of six dolutegravir arms (GS-US-380-1489), only half of the participants with confirmed VF (four of eight) were genotyped. All participants with PDVF were included in the RAP in the five remaining dolutegravir studies, though FLAMINGO showed the lowest rate of participants with virological non-response meeting PDVF cri-

Table 1. Week 48 Phase III clinical trials of the newest once-daily antiretroviral drugs in the first-line therapy in participants with HIV-1 infection: main characteristics

Third drug	Clinical trial	Design	Arm size (*n*)*	Female participants (%)	NRTIs	Comparator arm	High VL (%)**	Low CD4 (%)***	Efficacy: < 50 copies/ml at 48 weeks % (95% CI)♦
DTG	ΣSINGLE[21,22]	DB	414	16.0	3TC/ABC	EFV †	32.0	14.0	88% versus 81%; 7 (2-12)
	SPRING-2[8,9]	DB	411	15.0	2NRTIs††	RAL	28.0	13.0	88% versus 85%; 2.5 (–2.2-7.1)
	FLAMINGO[23]	OL	242	13.0	2NRTIs††	DRV/r	25.0	10.0	90% versus 83%; 7.1 (0.9-13.2)
	Σ‡ARIA[24,25]	OL	248	100.0&	3TC/ABC	ATV/r†	28.0	26.0	82% versus 71%; 10.5 (3.1-17.8)
	Σ‡GS-US-380-1489[10,11]	DB	315	10.0	3TC/ABC	BIC/FTC/TAF	16.0	10.0	93% versus 92%; –0.6 (3.6-–4.8)
	GS-US-380-1490[12,13]	DB	325	11.0	FTC/TAF	BIC	17.0	10.0	93% versus 89%; –3.5 (1-–7.9)

(Continue)

Table 1. Week 48 Phase III clinical trials of the newest once-daily antiretroviral drugs in the first-line therapy in participants with HIV-1 infection: main characteristics *(Continued)*

Third drug	Clinical trial	Design	Arm size (*n*)*	Female participants (%)	NRTIs	Comparator arm	High VL (%)**	Low CD4 (%)***	Efficacy: < 50 copies/ml at 48 weeks % (95% CI)♦
BIC	Σ‡GS-US-380-1489[10,11]	DB	314	9.0	FTC/TAF	DTG/3TC/ ABC	17.0	11.0	92% versus 93%; −0.6 (−4.8-3.6)
	‡GS-US-380-1490[12,13]	DB	320	13.0	FTC/TAF	DTG	21.0	14.0	89% versus 93%; −3.5 (−7.9-1)
EVG/c	Σ‡GS-US-292-0104 and 0111[14-16]	DB	866	15.0	FTC/TAF	FTC/TDF	23.0	13.0	92% versus 90%; 2 (−0.7-4.7)
RAL QD	ONCEMRK[29]	DB	531	17.0	FTC/TDF	RAL 400 mg BID	28.0	13.0	90% versus 90%; −0.4 (−4.9-4)
DRV/c	Ψ Σ‡AMBER[26]	DB	362	12.0	FTC/TAF	FTC/TDF	16.6	6,1	91% versus 88%; 2.7 (−1.6-7.1)
RPV	ECHO[30,31,32]	DB	346	23.0	FTC/TDF	EFV	48.0	33.0Φ	83% versus 83%; −0.4 (−5.9-5.2)♦♦
RPV	THRIVE[31-33]	DB	340	26.0	2NRTIs††	EFV	45.0	33.0Φ	86% versus 82%; 3.9 (−1.6-9.5)♦♦
	‡STaR[17-20]	OL	394	7.0	FTC/TDF	EFV	34.0	13.0	86% versus 82%; 4.1 (−1.1-9.2)
DOR	‡Drive-ahead[27]	DB	364	16.0	3TC/TDF	EFV†	20.0	12.0	84% versus 81%; 3.5 (−2-9)
	Drive-forward[28]	DB	383	17.0	2NRTIs††	DRV/r	22.0	11.0	84% versus 80%; 3.9 (−1.6-9.4)

VL: viral load; ABC: abacavir; 3TC: lamivudine; FTC: emtricitabine; TDF: tenofovir disoproxil fumarate; TAF: tenofovir alafenamide; DTG: dolutegravir; BIC: bictegravir; EVG/c: cobicistat-boosted elvitegravir; RAL: raltegravir; DRV/c: cobicistat-boosted darunavir; ATV/r: ritonavir-boosted atazanavir; EFV: efavirenz; RPV: rilpivirine; DOR: doravirine; DB: double-blind; OL: open-label.

*Number of participants in the arm that includes the study drug (randomized and treated).

**% of participants with VL >100.000 copies/mL.

***% of participants with<200 CD4+cells/µl.

†Combination therapy with coformulated NRTI: FTC/TDF.

††Participants received an open-label investigator-selected regimen of background NRTIs: SPRING-2 study: TDF plus FTC (59%) or ABC plus 3TC (41%); FLAMINGO study: TDF plus FTC (67%) or ABC plus 3TC (33%); THRIVE study: TDF plus FTC (60%), AZT plus 3TC (30%) or ABC plus 3TC (10%); DRIVE-FORWARD study: TDF plus FTC (87%), ABC plus 3TC (13%).

&41% African heritage.

ΣThis study excluded participants with positive hepatitis B surface antigen.

ΨThis study excluded participants with CD4≤50 cells/µl.

‡Fixed dose combination (FDC).

Φ% of participants with CD4<200 cells/µl in pooled ECHO and THRIVE data.

♦Efficacy of the study arm versus control arm; adjusted treatment difference, 95% confidence interval (CI). Intention-to-treat (ITT) US FDA-defined snapshot algorithm unless otherwise specified.

♦♦Intention-to-treat-time-to-loss of virological response (ITT-TLOVR)

Table 2. Definition rules for virological failure and resistance testing at week 48 in the Phase III clinical trials analyzed.

Third drug	Clinical trial (*n*)	VF definition (PDVF)	Criteria for resistance testing	Sample tested for resistance
DTG	Single (*n*=414)[21,22]	2 VL ≥50 copies/mL on or after week 24	2 VL ≥ 50 copies/mL on or after week 24	First
	Spring-2 (*n*=411)[8,9]	2 VL ≥50 copies/mL on or after week 24	2 VL ≥ 50 copies/mL on or after week 24	First
	Flamingo (*n*=242)[23]	2 VL >200 copies/mL on or after week 24	2 VL > 200 copies/mL after week 24	First
	Aria (*n*=248) [24,25]	2 VL ≥400 copies/mL on or after week 24*	2 VL ≥ 400 copies/mL on or after week 24	First
	GS-US-380-1489 (*n*=315)[10,11]	Confirmed virological rebound ≥ 50 copies/mL or last available HIV-1 RNA ≥ 50 copies/mL	2 VL ≥ 50 copies/mL with the second VL ≥ 200 copies/mL or≥200 copies/mL at week 48 or last study visit	Second
	GS-US-380-1490 (*n*=325)[12,13]	Confirmed virological rebound ≥ 50 copies/mL or last available HIV-1 RNA ≥ 50 copies/mL	2 VL ≥ 50 copies/mL with the second VL≥200 copies/mL or≥200 copies/mL at week 48 or last study visit	Second
BIC	GS-US-380-1489 (*n*=314)[10,11]	Confirmed virological rebound≥50 copies/mL or last available HIV-1 RNA ≥ 50 copies/mL	2 VL ≥ 50 copies/mL with the second VL ≥ 200 copies/mL or ≥200 copies/mL at week 48 or last study visit	Second
	GS-US-380-1490 (*n*=320)[12,13]	Confirmed virological rebound≥50 copies/mL or last available HIV-1 RNA ≥ 50 copies/mL	2 VL ≥ 50 copies/mL with the second VL ≥ 200 copies/mL or≥200 copies/mL at week 48 or last study visit	Second
EVG/c	GS-US-292-0104 and 0111 (*n*=866)[14-16]	VL ≥ 50 copies/mL and<1 $\log_{10}$ reduction from baseline at week 8, or VL≥50 copies/mL after previous suppression to < 50 copies/mL or>1 $\log_{10}$ increase from nadir	2 VL ≥ 50 copies/mL after achieving < 50 copies/mL and the second VL ≥ 400 copies/mL; or VL ≥ 400 copies/mL at week 48 or last study visit	Second
RAL QD	Oncemrk (*n*=531)[29]	VL ≥ 40 copies/mL by week 24 or 2 VL ≥ 40 copies/mL after initial < 40 copies/mL	VL ≥ 500 copies/mL	Second
DRV/c	AMBER (*n*=362)[26]	Confirmed < 1 $\log_{10}$ VL reduction from baseline and VL ≥ 50 copies/mL at week 8 , or VL ≥ 50 copies/mL after previous suppression to < 50 copies/mL or > 1 $\log_{10}$ VL increase from nadir or VL ≥4 00 copies/mL at endpoint or last study visit after week 8	VL ≥ 400 copies/mL	Any†

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Table 2. Definition rules for virological failure and resistance testing at week 48 in the Phase III clinical trials analyzed. *(Continued)*

Third drug	Clinical trial (*n*)	VF definition (PDVF)	Criteria for resistance testing	Sample tested for resistance
RPV	ECHO (*n*=346)[30-32]	Never achieved 2 VL < 50 copies/mL and ≥ 0·5 $\log_{10}$ above nadir or 2 VL ≥ 50 copies/mL after 2 VL < 50 copies/mL (or single when last available)	Never achieved 2 VL < 50 copies/mL and ≥0·5 $\log_{10}$ above nadir or 2 VL ≥ 50 copies/mL after 2VL < 50 copies/mL (or single when last available)	First
	Thrive (*n*=340)[31-33]	Never achieved 2 VL < 50 copies/mL and ≥ 0.5 $\log_{10}$ above nadir or 2 VL ≥ 50 copies/mL after 2 VL < 50 copies/mL (or single when last available)	Never achieved 2 VL <50 copies/mL and ≥0.5 $\log_{10}$ above nadir or 2 VL ≥ 50 copies/mL after 2 VL <50 copies/mL (or single when last available)	First
	STaR (*n*=394)[17-20]	VL ≥ 50 copies/mL and < 1 $\log_{10}$ reduction from baseline at week 8, or VL ≥ 50 copies/mL after previous suppression to < 50 copies/mL, or > 1 $\log_{10}$ increase from nadir	VL ≥ 400 copies/mL at week 48 or last study visit (at or after week 8) or suboptimal virological response (<1 $\log_{10}$ decrease in VL from baseline at week 8 and confirmed at the subsequent visit) or confirmed VF	Second
DOR	Drive-ahead (*n*=364)[27]	Confirmed VL ≥ 200 copies/mL at week 24 or week 36 or confirmed VL ≥ 50 at week 48 or confirmed VL ≥ 50 copies/mL after initial VL < 50 copies/mL	VL > 400 copies/mL**	Any††
	Drive-forward (*n*=383)[28]	Confirmed VL ≥ 200 copies/mL at week 24 or week 36 or confirmed VL ≥ 50 at week 48 or confirmed VL ≥ 50 copies/mL after initial VL < 50 copies/mL	VL > 400 copies/mL***	Second

n denotes number of participants referred to overall of each treatment arm; VL: viral load; PDVF: protocol-defined virological failure; VF: virological failure; DTG: dolutegravir; BIC: bictegravir; EVG/c: cobicistat-boosted elvitegravir; RAL: raltegravir; DRV/c: cobicistat-boosted darunavir; RPV: rilpivirine; DOR: doravirine
*VF not defined throughout ARIA study. Instead, criteria for virological withdrawal were defined as specified above.
**The plasma sample collected for resistance testing from the VF visit and the confirmation visit was tested for resistance testing provided the VL was > 400 copies/mL.
***Sample from the VF confirmation visit was sent for resistance testing if VL > 400 copies/mL or, if not available, from early discontinuation visits.
†PDVF with VL≥400 copies/mL at failure (preferably confirmed, or otherwise at unconfirmed virological failure time point) or at later time points.
††Both samples (first and second) or either one, if VL > 400 copies/mL

teria (2/15, 13.3%). In both bictegravir arms analyzed (GS-US-380-1489/1490), up to half of the participants with PDVF met the predefined criteria for genotyping (one participant of three and seven of 14, respectively). In the elvitegravir/cobicistat arm, only 19/31 (61.3%) participants with PDVF met the resistance criteria and five of them were not genotyped because they resuppressed without any treatment change; therefore, only 45.2% of the participants with PDVF were eventually genotyped.

The raltegravir once-daily study showed the highest rate of inconsistency between the number of participants with PDVF and those included in the RAP. Only 14 of 36 (39%) participants with PDVF were eventually genotyped. This was related to the choice of the highest threshold for genotyping (≥ 500 copies/mL of HIV-1 RNA) among all analyzed studies.

All participants with PDVF were genotyped in the AMBER study (darunavir/cobicistat), though only half (8/16) of those with virological non-response were considered VF. All participants meeting PDVF criteria were genotyped in the rilpivirine studies ECHO and THRIVE, but only 62.5% (20/32) in STaR. This was probably related to the choice of a highest threshold defined for genotyping (≥ 400 copies/mL) in the latter, contrary to ≥ 50 copies/mL in the first two studies.

Table 3. Main virological outcomes and HIV resistance analysis findings at week 48 in the Phase III clinical trials analyzed

Third drug	Clinical trial (*n*)¶	Virological non-response, VL≥50 copies/mL, week 48; *n* (%)*	Confirmed VL>200 copies/mL, week 48; *n* (%)	PDVF *n* (%)	Met criteria for inclusion in RAP, *n* (%)	Met PDVF definition but not included in RAP, *n* (%)	Failed amplification *n* (%)	Emergent resistance: any, *n* (%)	Emergent resistance: third drug, *n* (%)	Emergent resistance: NRTIs, *n* (%)
DTG	Single (*n*=414)[21,22]	21 (5.1)	2 (0.5)	18 (4.3)	18 (4.3)	0	9 (2.2)	0	0	0
	Spring-2 (*n*=411)[8,9]	20 (4.9)	7 (1.7)	20 (4.9)	20 (4.9)	0	8 (2.0)	0	0	0
	Flamingo (*n*=242)[23]	15 (6.2)	2 (0.8)	2 (0.8)	2 (0.8)	0	0	0	0	0
	ARIA (*n*=248)[24,25]	16 (6·4)	NA	6 (2·4)	6 (2·4)	0	0	0	0	0[&]
	GS-US-380-1489 (*n*=315)[10,11]	8 (2.5)	4 (1.2)	8 (2.5)	4 (1.3)	4 (1.3)	1 (0.3)	0	0	0
	GS-US-380-1490 (*n*=325)[12,13]	4 (1.2)	NA	4 (1.2)	5 (1.5)[†]	NA	0	0	0	0
BIC	GS-US-380-1489 (*n*=314)[10,11]	3 (1.0)	1 (0.3)	3 (1.0)	1 (0.3)	2 (0.6)	0	0	0	0
	GS-US-380-1490 (*n*=320)[12,13]	14 (4.4)	7 (2.1)	14 (4.4)	7 (2.1)	7 (2.1)	0	0	0	0
EVG/c	GS-US-292-0104 and 0111 (*n*=866)[14-16]	31 (3.6)	NA	31 (3.6)	19 (2.2)[††]	17 (2.0)	0	7 (0.8)	5 (0.5)[&&]	7 (0.8)[&&&]
RAL QD	ONCEMRK (*n*=531)[30]	29 (5.5)**	6 (1.1)	36 (6.8)	14 (2.6)	22 (4.1)	4 (0.7)	5 (0.9)	4 (0.7)[&&]	5 (0.9)[&&&]
DRV/c	AMBER (*n*=362)[26,27]	16 (4.4)	8 (2.2)	8 (2.2)	8 (2.2)[‡]	0	0	0	0	0[&&&&]
RPV	ECHO (*n*=346)[31-33]	38 (11.0)***	NA	45 (13.0)	45 (13)	0	5 (1.4)	29 (8.3)	26 (7.5)[♦]	28 (8) [♦♦]
	THRIVE (*n*=340)[32-34]	24 (7.1)***	NA	27 (7.9)	27 (8)	0	5 (1.5)	15 (4.4)	13 (3.8)[♦]	14 (4.1)[♦♦]
	STaR (*n*=394)[17-20]	32 (8.1)	NA	32 (8.1)	20 (5.1)	12 (3.0)	0	17 (4.3) [Φ]	16 (4.1)[♦]	16 (4.1)[♦♦]

(Continue)

Table 3. Main virological outcomes and HIV resistance analysis findings at week 48 in the Phase III clinical trials analyzed *(Continued)*

Third drug	Clinical trial (*n*)¶	Virological non-response, VL≥50 copies/mL, week 48; *n* (%)*	Confirmed VL>200 copies/mL, week 48; *n* (%)	PDVF *n* (%)	Met criteria for inclusion in RAP, *n* (%)	Met PDVF definition but not included in RAP, *n* (%)	Failed amplification *n* (%)	Emergent resistance: any, *n* (%)	Emergent resistance: third drug, *n* (%)	Emergent resistance: NRTIs, *n* (%)
DOR	Drive-ahead (*n*=364)[28]	39 (10.7)	12 (3.3)	22 (6.0)	13 (3.6)‡‡	9 (2.5)	1 (0.2)ᵠ	9 (2.5)	7 (1.9)♦	9 (2.5)♦♦ ≤
	Drive-forward (*n*=383)[29]	43 (11.2)	7 (1.8)	19 (5.0)	7 (1.8)‡‡‡	12 (3.1)	1 (0.3)ᵠᵠ	1 (0.3)≤≤	1 (0.3)	1 (0.3)

VL: viral load; NRTI, nucleos (t) ide reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; RAP: resistance analysis population; PDVF: protocol-defined virological failure; DTG: dolutegravir; BIC: bictegravir; EVG/c: cobicistat-boosted elvitegravir; RAL: raltegravir; DRV/c: cobicistat-boosted darunavir; RPV: rilpivirine; DOR: doravirine; NA: not available

¶n denotes number of participants referred to overall of each treatment arm.

*ITT US FDA-defined snapshot algorithm unless otherwise specified.

**Analysis done by VF snapshot algorithm, defined as VL ≥ 40 copies/mL at week 48.

***ITT - time-to-loss of virological response (TLOVR).

&K219Q (1), E138G (1) were revealed at withdrawal but did not reduce susceptibility to any of the antiretroviral drugs tested.

&&Integrase emergent mutations (number of participants): GS-US-292-0104 and 0111 studies: T66A (1), E92Q (2), Q148R+T66I/A (1), N155H (1); ONCEMRK study: L74M+E92Q (1), N155H (1), V151I+N155H (1), N155H+I203M (1).

&&&NRTI emergent mutations (number of participants): GS-US-292-0104 and 0111 studies: M184V/I (6), M184V/I+K65R (1); ONCEMRK study: M184V (3), M184M/I/V (1), V118I+M184M/I/V (1).

&&&&M184I/V was detected pretreatment by deep sequencing as a minority variant (9.4%).

†One participant without PDVF was included in RAP.

††5 participants who resuppressed HIV-1 RNA to<50 copies/mL while maintaining study drugs were not genotyped. Only 14 participants were genotyped.

‡One participant was released after database lock and was resuppressed at following unscheduled visit so was missing for the week 48 analyses. Of the eight PDVF, two showed response and six virologic failures as defined by FDA snapshot.

‡‡13 of 22 participants meeting PDVF and 10 of 35 participants discontinuing for reasons other than PDVF were included in RAP. In addition, five participants included in RAP were not tested for resistance for various reasons (protocol deviation or lost to follow-up).

‡‡‡7 of 19 participants meeting PDVF and 2 of 40 participants discontinuing without PDVF were included in RAP.

♦Most frequent NNRTI emergent mutations (number of participants): ECHO study: E138K (18), K101E (5), Y181C (5); THRIVE study: E138K (10), K101E (3), V189I (2); STaR study: Y181C/I (8), E138K/Q (6), K101E (5); DRIVE-AHEAD study: V106I/V/A/M/T (4), F227C/R (4).

♦♦Most frequent NRTI emergent mutations (number of participants): ECHO study: M184V/I (26), K65R (3); THRIVE study: M184V/I (12); STaR study: M184V/I (15), K65R/N (3); DRIVE-AHEAD study: M184V (4), K65R/K (2).

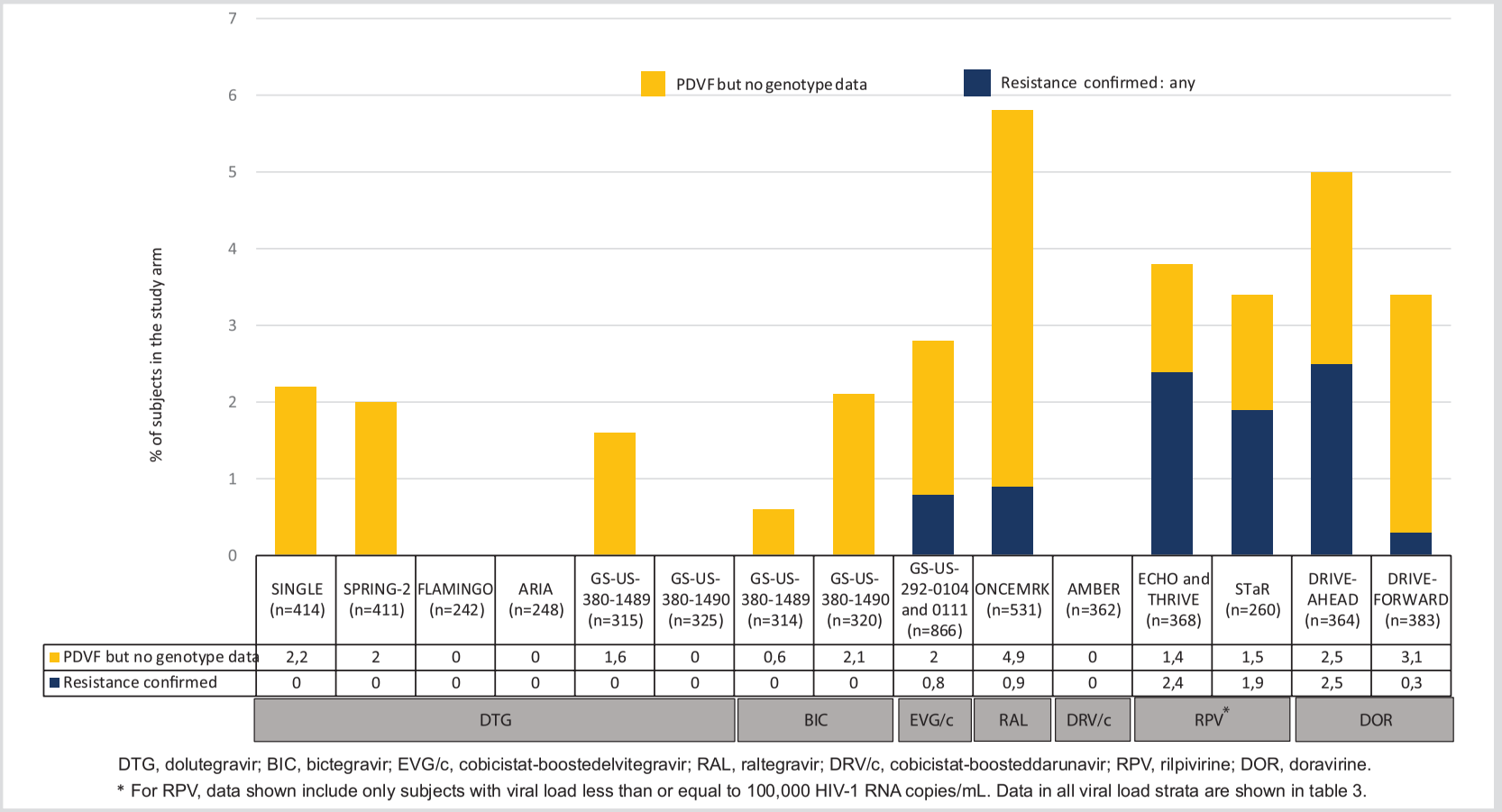
≤Two the nine participants who discontinued without PDVF, developed resistances against NRTI.

≤≤One of the two participants who discontinued at week 24 without PDVF, developed resistances against DOR (V106I, H221Y, F227C) and FTC (M184V).

ΦAny emergent anchor or NRTI resistance by baseline HIV-1 RNA: 5/260 in VL<100.000copies/mL, 5/98 in VL>100.000-500.000copies/mL, 7/36 in VL>500.000 copies/mL.

ᵠOne of 10 participants who discontinued without PDVF, failed amplification.

ᵠᵠOne participant meeting PDVF, not sample collected for resistance testing, due to trial site error



DTG, dolutegravir; BIC, bictegravir; EVG/c, cobicistat-boostedelvitegravir; RAL, raltegravir; DRV/c, cobicistat-boosteddarunavir; RPV, rilpivirine; DOR, doravirine.

* For RPV, data shown include only subjects with viral load less than or equal to 100,000 HIV-1 RNA copies/mL. Data in all viral load strata are shown in table 3.

Figure 1. *Percentages of participants with drug resistance mutations selected at virological failure, and participants meeting PDVF criteria but with no genotype data available at 48 weeks in the Phase III studies analyzed.*

Finally, in DRIVE-AHEAD (doravirine), 13 of 22 (59.1%) participants with PDVF were genotyped; in addition, 10 out of 35 participants discontinuing for reasons other than PDVF, were included in RAP. In DRIVE-FORWARD, only seven of 19 (37%) participants with PDVF plus two of 40 participants who discontinued for reasons other than PDVF with last HIV-1 RNA > 400 copies/mL were genotyped.

No resistance was selected against the third drug in any participant in the studies with dolutegravir (*n* = 1955 participants), bictegravir (*n* = 634), or darunavir/cobicistat (*n* = 362). No resistance against the backbone NRTIs was selected with either dolutegravir, bictegravir, or darunavir/cobicistat. Two participants assigned to dolutegravir in the ARIA study had either K219Q or E138G in the reverse transcriptase, with no reduced susceptibility to any study drugs. One participant (1/362) treated with darunavir/cobicistat was found to have one NRTI resistance mutation (M184I/V), but it was detected in a pre-treatment sample by deep sequencing.

Resistance against the third drug and backbone NRTIs was commonly selected in participants with PDVF and genotype data available in the elvitegravir/cobicistat study. Half of the participants (7/14) genotyped had resistance against the NRTIs and five had resistance in the integrase as well. The rate of participants with any resistance selected at failure was also high among those with PDVF on raltegravir (five of 10, 50% with resistance against NRTIs, four with simultaneous integrase resistance mutations) with a successfully amplified genotype. This is particularly worrisome as this study showed the highest discordance between PDVF and RAP populations, with 22 of 36 participants with PDVF not genotyped due to having an HIV-1 RNA < 500 copies/mL.

Sixty-one of 1080 (5.6%) participants included in rilpivirine studies (ECHO, THRIVE, and STaR) with PDVF and HIV-1 genotyping data available selected for some resistance against NNRTIs (55 of 61) and against the backbone NRTIs (58 of 61). 10 of 747 (1.3%) participants treated with doravirine selected any resistance against NNRTIs and against the backbone NRTIs.

A variable number of participants meeting the RAP criteria failed genotype amplification due to technical issues, protocol violations, or trial site errors (Table 2). Overall, there was an inverse correlation between the threshold used in HIV-1 RNA for amplification and the rate of participants with amplification failure. By contrast, the study with highest threshold for resistance testing (raltegravir, HIV-1 RNA ≥ 500 copies/mL), unexpectedly disclosed a relevant rate of amplification failure (four of 14 participants who were genotyped). We found a strong evidence of an association between the higher HIV-1 RNA threshold for genotyping and increasing rates of participants with PDVF that was not eventually genotyped: < 50 copies/mL 0/110 (0%), < 200 copies/mL, 13/32 (40·6%), <400 copies/mL 50/118 (42.4%), and < 500 copies/mL 22/36 (61.1%), $p < 0.001$ (Cochran–Armitage test).

Discussion

In this systematic review of week 48 virological outcomes in 16 treatment arms including 6175 participants in 14 Phase III non-inferiority RCTs of treatment-naïve HIV-1-infected participants, the rates of virological non-response were low in all included RCTs, being lower in INSTI- or PI-based than in NNRTI-containing regimens. Unexpectedly, despite being studies mainly designed for drug registration and approval, we found a high discrepancy in the criteria used to designate PDVF and RAP populations among the studies, with thresholds of plasma HIV-1 RNA ranging from 40 to 50, 200, 400, and even 500 copies/mL. The higher the threshold above which genotyping was performed in the studies, a significantly higher rate of participants with confirmed PDVF was not genotyped in a given study.

While all participants with virological non-response were considered PDVF in five studies (SPRING-2, GS-US-380-1489 and -1490, GS-US-292-0104/0111, and STaR), the remaining studies commonly included <50% of participants with virological non-response as PDVF, with the lowest percentages in FLAMINGO (13.3%), ARIA (37.5%), and DRIVE-FORWARD (44.2%).

In addition, the definitions of PDVF were frequently different than those chosen for the inclusion in the RAP, and therefore, a variable number of participants with confirmed VF were not subsequently considered for genotyping. Only five (out of six) dolutegravir studies, the darunavir/cobicistat one, and the rilpivirine ECHO and THRIVE studies genotyped all participants with PDVF. However, approximately 50% or less of the participants with PDVF were included in the RAP population (and therefore genotyped) in the GS-US-380-1489 dolutegravir arm, both bictegravir studies, and the elvitegravir/cobicistat one. Only 39% of participants with PDVF in the raltegravir once-daily study, 37% in the DRIVE-FORWARD doravirine study (the lowest rate), 62.5% in the rilpivirine STaR study, and 59% in the DRIVE-AHEAD study were genotyped. Not surprisingly, this was related to the choice of the highest threshold of HIV-1 RNA to genotype the samples at VF: 500 copies/

mL in the raltegravir study and 400 copies/mL in both doravirine DRIVE studies.

This opens up the possibility that variable degrees of HIV resistance at VF may have evolved in participants with confirmed VF but which did not undergo genotypic analysis and adds uncertainty in the interpretation of the trial results.

This is particularly worrisome with drugs that have a low barrier against resistance development and in which, hence, HIV-1 resistance is not infrequently found in the genotypes performed at VF. These drugs include elvitegravir/cobicistat, raltegravir, and rilpivirine, showing selection of HIV-1 resistance against both the third drug and the NRTIs used in the backbone in approximately 50% of the participants with PDVF and genotypes successfully performed. Of particular concern is the raltegravir once-daily study, with 50% (5/10) of participants genotyped successfully harboring mutations both in the integrase and reverse transcriptase, but with the highest rate of inconsistency between PDVF and RAP populations, with only 39% of participants with PDVF included in the RAP analysis.

The dolutegravir, bictegravir, and cobicistat-boosted darunavir studies reported no emergent resistance against the third drugs evaluated or the backbone NRTIs. The strength of this evidence driven by the number of individuals included in the analysis is currently very high with dolutegravir, followed by bictegravir and was lower with darunavir/cobicistat. However, prior data with darunavir/ritonavir in the ARTEMIS study add further evidence on the absence of resistance selection with this drug[34].

A variable number of participants included in the RAP are not eventually genotyped for a variety of reasons, mainly spontaneous resuppression with no treatment change. In some cases, pharmacokinetic studies confirm low or absent plasma levels of the study drugs along the transient VF, therefore, confirming treatment non-adherence. However, this does not preclude resistance selection. Some cases do not have a valid amplification due to technical issues or trial site errors. This information is not easily obtained or is lacking in most of the presentations/publications and should be more clearly depicted in the resistance analysis tables to allow a complete interpretation of the resistance shown in the studies.

In addition, the failure to detect resistance (by standard population genotyping amplification) does not necessarily rule out the existence of resistance, and having had a PDVF while receiving low resistance barrier drugs have clinical implications for future treatment choices. Once resistance has developed to a drug or drug class through cross-resistance, resistant viruses are archived in lymphoid cells, and responses to the drug are compromised indefinitely[35].

When selecting a subsequent regimen in participants with confirmed VF despite the lack of genotypic resistance tests, these limitations should be borne in mind, especially when considering some simplification strategies including dual therapies (such as dolutegravir/lamivudine, dolutegravir/rilpivirine, or cabotegravir/rilpivirine long-acting regimens). A twice-daily dose of DTG should even be considered in some of these cases with confirmed VF on an INSTI regimen despite the lack of genotype data available, particularly when the activity of other drugs in future regimens is compromised.

The choice of higher thresholds of HIV-1 RNA to perform a genotyping is usually attributed to the lack of validation of these FDA-approved tests in participants with < 1000 copies/mL, and the possibility of rendering inaccurate genotypic results with lower viral loads.[6] Routine and in-house assays can, however, be adapted to perform at low viral load levels with high success rates. In a recent analysis with 4915 samples, 88% of low-level viremia (< 1000 copies/mL) resistance assays produced useable sequences, with higher success at higher VL. Up to 70% of samples with HIV-1 RNA 100-199 copies/mL and 79-91% with 200-400 copies/mL had a valid amplification and, of interest, the results appeared predictive of future virological outcomes[36,37]. Therefore, test limitations are no longer a reason to hinder genotyping samples from participants with lower level viremia at VF in Phase III clinical trials. While not validated assays might not be acceptable by the regulatory agencies, the information should be additionally offered in all registrational Phase III studies.

The effect of low-range low-level viremia (51-199 copies per mL) on subsequent failure of ART remains unclear[38]. However, a recent analysis has shown that the Cox proportional hazards analysis of the association between this stratum of low-level viremia and confirmed VF on the first-line ART is 2.0 (95% CI=1.8-2.2), increasing the risk with increased ranges of low-level viremia[37]. The risk was significantly increased even after a single measurement of low-range low-level viremia of 51-199 copies/mL.

Current guidelines define VF as a confirmed viral load > 200 copies/ml, a threshold that eliminates most cases of apparent viremia caused by viral load blips or assay variability.[7] Therefore, at a minimum, genotyping should be attempted on all participants with confirmed VF at this threshold in clinical trials.

Further, variability exists in trial methodology as some trials perform the genotype on the first sample at

VF while others do it in the second or last confirmatory sample (Table 1). One trial performed a genotype in both the first and second samples[27]. The question is not trivial, as using the second confirmatory sample may allow for variable periods of low or intermediate viral replication before the analysis (that may last up to some weeks even in highly controlled RCTs) and lead to the accumulation of further HIV resistance.

An elegant *ad hoc* analysis of elvitegravir/cobicistat studies has shown that first failure found fewer participants with emergent resistance than the analysis done at the later confirmation of VF[39]. The first failure timepoint underestimates emergent resistance mutations and may not fully describe the extent of resistance that developed at the time of a subsequent regimen switch. Therefore, an agreement must be reached in all clinical trials to perform the genotype in the same timepoint sample at VF to allow a fair comparison, with the best results obtained at the last confirmatory sample.

A limitation of our analysis was the incomplete retrieval of data regarding confirmed VF with HIV-1 RNA > 200 copies/mL at week 48 in those trials without this predefined limit, according to the FDA-defined VF. This lack of information has hindered the homogenization of VF threshold in each trial to perform an even comparison of virological outcomes among all RCTs included in the systematic review. Moreover, all analyses used population sequencing, which does not detect low-frequency mutations.

In summary, there is a significant variation in the definitions of VF and criteria predefined for resistance testing in pivotal registration randomized studies of antiretroviral agents in treatment-naïve participants. Therefore, a relevant proportion of participants with confirmed VF do not undergo an HIV genotype evaluation. We recommend the use of common standardized criteria in all studies to provide an accurate direct comparison and suggest that all participants with confirmed VF and any VL - or at least a VL > 200 copies/mL - should undergo genotypic analysis. This would reduce the uncertainty of resistance selection and its potential clinical impact in those participants with confirmed VF without a genotype. The sample used for genotyping should also be standardized, and data suggest that using the second or confirmatory sample would be optimal.

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References

1. White K, Raffi F, Miller M. Resistance analyses of integrase strand transfer inhibitors within phase 3 clinical trials of treatment-naive patients. Viruses. 2014;6:2858-79.
2. Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264-9.
3. European AIDS Clinical Society. European Guidelines for Clinical Management and Treatment of HIV-1-Infected adults in Europe, version 9.0. Available from: http://www.eacsociety.org/files/guidelines_9.0-english.pdf. [Last accessed on 2018 May 5].
4. AIDS Study Group GeSIDA of the Spanish Society of Infectious Diseases and Clinical Microbiology and the National AIDS Plan. Executive summary of the GESIDA/National AIDS Plan Consensus Document on Antiretroviral Therapy in Adults Infected by the Human Immunodeficiency Virus. Enferm Infecc Microbiol Clin 2018 (In Press).
5. Günthard HF, Saaq 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.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Last accessed on 2018 May 5].
7. Lalama C, Jennings C, Johnson V, et al. Comparison of three different fda-approved plasma hiv-1 rna assay platforms confirms the virologic failure endpoint of 200 copies per milliliter despite improved assay sensitivity. J Clin Microbiol. 2015;53:2659-66.
8. Raffi F, Rachlis A, Stellbrink H, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet. 2013;381:735-43.
9. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily Dolutegravir (DTG; S/GSK1349572) is Non-inferior to Raltegravir (RAL) in Antiretroviral Naive Adults. 48 Week Results from SPRING-2 (ING113086). Washington DC: 19th International AIDS Conference, July 22-27; 2012.
10. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicenter, phase 3, randomised controlled non-inferiority trial. Lancet. 2017;390:2063-72.
11. Gallant J, Lazzarin A, Mills A, et al. A Phase 3 Randomised Controlled Clinical Trial of Bictegravir in a Fixed Dose Combination B/F/TAF, vs DTG/ABC/3TC in Treatment-Naïve Adults at Week 48. Paris, France: 9th International AIDS Society Conference on HIV Science (IAS 2017), July 23-26; 2017.
12. Sax P, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicenter, phase 3, non-inferiori. Lancet. 2017;390:2073-82.
13. White K, Kulkarni R, Willkom M, et al. Pooled Week 48 Efficacy and Baseline Resistance: b/F/TAF in Treatment-Naïve Patients. Boston: 25th Conference on Retroviruses and Opportunistic Infections (CROI 2018), March, 4-7; 2018.
14. Sax P, Wohl D, Yin M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385:2606-15.
15. Orkin C, Koenig E, Clarke A, et al. Improved Safety and Efficacy of TAF vs TDF Single-Tablet Regimen in HIV-1 Treatment-Naïve Women Through Week 48. [Abstract PE7/13]. Barcelona, Spain: 15th European AIDS Conference (EACS), October 21-24; 2015.
16. Miller MD, Margot N, Kitrinos KM, et al. Integrated Analysis of Emergent Drug Resistance through 48 Weeks from Clinical Studies of HIV-1 Treat-

ment-naive subjects Receiving E/C/F/TAF. Barcelona, Spain: 15th European AIDS Conference (EACS), October 21-24; 2015.
17. Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomised clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected adults. AIDS. 2014;28:989-97.
18. Porter D, Kulkarni R, Fralich T, Miller M, White K. Characterization of HIV-1 drug resistance development through week 48 in antiretroviral naive subjects on rilpivirine/emtricitabine/tenofovir DF or efavirenz/emtricitabine/tenofovir DF in the STaR study (GS-US-264-0110). J Acquir Immune Defic Syndr. 2014;65:318-26.
19. Cohen C, Wohl D, Henry K, et al. STaR study: association of Efficacy Outcomes with Baseline HIV-1 RNA and CD4 Count and Adherence Rate for the Single-tablet regimens Rilpirivine/Emtricitabine/Tenofovir DF and Efavirenz/Emtricitabine/Tenofovir DF in ART-naïve Adults. [Abstract 671]. San Francisco, CA: ID Week 2013, October 4; 2013.
20. Porter D, Kulkarni R, Fralich T, Miller M, White K. Primary and Secondary Analyses of Emergent Drug Resistance through week 48 from the STaR study: rilpivirine/Emtricitabine/Tenofovir DF versus efavirenz/emtricitabine/tenofovir DF Single-tablet Regimens. [Abstract 30]. Toronto, Canada: International Workshop on HIV and Hepatitis Virus Drug Resistance and Curative Strategies June, 4-8; 2013.
21. Walmsley S, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;369:1807-18.
22. Walmsley S, Antela A, Clumeck N, et al. Dolutegravir (DTG; S/GSK1349572) + Abacavir/Lamivudine Once Daily Statistically Superior to Tenofovir/Emtricitabine/Efavirenz: 48-Week Results-SINGLE. San Francisco: 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 9-12; 2012.
23. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;383:2222-31.
24. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label. Lancet HIV. 2017;4:e536-46.
25. Orrell C, Hagins D, Belonosova E, et al. Superior Efficacy of Dolutegravir/Abacavir/Lamivudine FDC Compared With Ritonavir-Boosted Atazanavir Plus Tenofovir Disoproxil Fumarate/Emtricitabine FDC in Treatment-Naive Women With HIV-1 Infection: aria Study. Durban, South Africa: 21st International AIDS Conference, July 18-22; 2016.
26. Eron JJ, Orkin C, Gallant J, et al. A week 48 randomized phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. AIDS. 2018; 32(11):1431-42.
27. Squires K, Molina JM, Sax P, et al. Fixed Dose Combination of Doravirine/Lamivudine/TDF is Non-inferior to Efavirenz/Emtricitabine/TDF in Treatment-naïve Adults with HIV-1 Infection: week 48 Results of the Phase 3 DRIVE-AHEAD study. [Abstract TUAB0104LB]. Paris, France: 9th IAS Conference on HIV Science (IAS 2017), July 23-26; 2017.
28. Molina JM, Squires K, Sax P, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV. 2018;5:e211-20.
29. Cahn P, Kaplan R, Sax P, et al. Raltegravir 1200 mg once daily versus raltegravir 400mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV. 2017;4:e486-94.
30. Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet. 2011;378:238-46.
31. Cohen C, Molina J-M, Jayaweera D, et al. Relationship between Combination of Baseline Viral Load and CD4 Cell Count, and Week 48 or 96 Responses to Rilpivirine (RPV) or Efavirenz (EFV) in treatment-naïve HIV-1-Infected Adults: pooled Analysis from the Phase III ECHO and THRIVE trials. Seattle-WA: Presented at: 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012), March 5-8; 2012.
32. Rimsky L, Van Eygen V, Hoogstoel A, et al. 96-Week resistance analyses of rilpivirine in treatment-naive, HIV-1-infected adults from the ECHO and THRIVE Phase III trials. Antivir Ther. 2013;18:967-77.
33. Cohen C, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet. 2011;378:229-37.
34. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS. 2008;22:1389-97.
35. Bartlett J, Buda J, von Scheele B, et al. Minimizing resistance consequences after virologic failure on initial combination therapy: a systematic overview. J Acquir Immune Defic Syndr. 2006;41:323-31.
36. Gonzalez-Serna A, Min J, Woods C, et al. Performance of HIV-1 drug resistance testing at low-level viremia and its ability to predict future virologic outcomes and viral evolution in treatment-naive individuals. Clin Infect Dis. 2014;58:1165-73.
37. Hermans L, Moorhouse M, Carmona S, et al. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. Lancet Infect Dis. 2018;18:188-97.
38. Taiwo B, Gallien S, Aga E, et al. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis. 2011;204:515-20.
39. White K, Kulkarni R, Miller M. Analysis of early resistance development at the first failure timepoint in elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate-treated patients. J Antimicrob Chemother. 2015; 70:2632-8.