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Definition of Virological Endpoints Improving the Design of Human Immunodeficiency Virus (HIV) Cure Strategies Using Analytical Antiretroviral Treatment Interruption

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Background. Analytical treatment interruption (ATI) is the gold standard in HIV research for assessing the capability of new therapeutic strategies to control viremia without antiretroviral treatment (ART). The viral setpoint is commonly used as endpoint to evaluate their efficacy. However, in line with recommendations from a consensus meeting, to minimize the risk of increased viremia without ART, trials often implement short ATI phases and stringent virological ART restart criteria. This approach can limit the accurate observation of the setpoint.

Methods. We analyzed viral dynamics in 235 people with HIV from 3 trials, examining virological criteria during ATI phases. Time-related (eg time to rebound, peak, and setpoint) and viral load magnitude-related criteria (peak, setpoint, and time-averaged AUC [nAUC]) were described. Spearman correlations were analyzed to identify (1) surrogate endpoints for setpoint and (2) optimal virological ART restart criteria mitigating the risks of ART interruption and the evaluation of viral control.

Results. Comparison of virological criteria between trials showed strong dependencies on ATI design. Similar correlations were found across trials, with nAUC the most strongly correlated with the setpoint, with correlations >0.70. A threshold >100 000 copies/mL for 2 consecutive measures is requested as a virological ART restart criterion.

Conclusions. Our results are in line with recommendations and emphasize the benefits of an ATI phase >12 weeks, with regular monitoring, and a virological ART restart criterion of 10 000 copies/mL to limit the risk for patients while capturing enough information to keep nAUC as an optimal proxy to the setpoint.

Keywords. analytical treatment interruption; clinical trials; antiretroviral treatment; HIV cure; virological endpoint.

Antiretroviral treatment (ART) interruption is still considered in the evaluation of strategies such as immunotherapies or therapeutic vaccines [1] aimed to control human immunodeficiency virus (HIV) replication without ART [2–7]. While accepted in a context of clinical trials involving people with HIV (PWH) [8, 9], treatment interruption should be carefully monitored and several recommendations have been proposed to limit risks, in terms of mortality, disease progression, HIV transmission, and emergence of drug resistance [10, 11]. These recommendations led to the development of analytical treatment interruptions (ATIs) [10]. Therefore, it is of the utmost

importance to optimize the design of ATI trials to maximize information while minimizing risk exposure [12]. As recently published in a consensus paper [10] and largely discussed [12–16], there is an agreement that the design, choice of study endpoints, and ART restart criteria highly depend on the study objectives. Specifically, ATIs can be used either to demonstrate the properties of strategies to (1) cure HIV by evaluating their efficacy in delaying HIV rebound [17, 18] or (2) control viral replication without ART by quantifying their ability to reduce viral setpoint or to generate post-treatment controllers [19]. Consequently, 2 types of criteria are usually considered as virological endpoints, each associated with an objective: the time to viral rebound (TTR) and the setpoint (ie, the relatively stable level of HIV RNA) after rebound [10, 20], respectively. As recently studied [12], when the outcome of interest is the TTR, the viral load (VL) threshold for ART restart can be set low to limit risks (eg 1000 copies/mL). However, it could impair the assessment of viral replication control as some elites and post-treatment controllers might not be identified [5, 19, 21]. On the other hand, studies using setpoint as an endpoint require longer ATI periods with higher thresholds for ART restart, leading to an increased risk of HIV transmission and

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side effects. Thus, while TTR could be easily determined in ATI studies, assessing the viral replication setpoint, a proxy of viral rebound control, remains challenging. Therefore, establishing optimal ATI phase designs for setpoint studies that mitigate the risks associated with treatment interruption and viral control assessment is essential.

In the present study, we analyzed several virological parameters of viral rebound kinetics during ATI in different clinical trials of immunotherapeutics in chronic PWH. This study had a double objective. The first was to identify potential surrogate endpoints predictive of viral setpoints. The second was to validate the recommendations of a consensus meeting [10] on setpoint studies, about the duration of ATI, sampling frequency, and VL threshold for ART restart criteria.

METHODS

Clinical Trial Data

This study included individual data from participants involved in 3 different trials on PWH, including 2 therapeutic vaccine trials—(1) the VRI02 ANRS 149 LIGHT trial [22] (NCT01492985, and labeled LIGHT) and (2) the ANRS/VRI DALIA trial [23–25] (NCT00796770, and labeled DALIA)—and 1 trial testing an interleukin 2 (IL-2)–immunotherapeutic strategy, the ANRS 118 ILIADÉ trial [26] (NCT00071890, and labeled ILIADÉ). All trials comprised an ATI phase to evaluate the virological efficacy of these strategies in maintaining low viral replication after ART interruption. As described in Figure 1, participants were involved in a 12-week ATI phase in LIGHT, a 24-week ATI phase in DALIA, and a 48-week ATI phase in ILIADÉ, with VL measurements performed every 2 weeks, 1 to 4 weeks, and 8 weeks, respectively. A full description of these 3 trials, including study design, VL-based ART restart criteria, study endpoints, and ethic statements can be found in the [Supplementary Materials Methods: Clinical trial data](#). See [Supplementary Figure 2](#) for flowcharts of participants in this study.

Definition of Virological Criteria

The virological data collected in the aforementioned studies were analyzed considering 8 criteria summarizing viral rebound dynamics during ATI. These criteria were selected from those most frequently used as virological endpoints in ATI studies [5, 10, 19, 22, 27] or extensively investigated in similar statistical studies [12, 13, 16, 17, 28]. Specifically, we included 3 criteria describing the VL magnitude: (1) peak VL, (2) setpoint, and (3) time-averaged area under the curve (nAUC) (ie, AUC divided by the duration of ATI phase). A normalized version of the AUC was used to adjust for ATI duration and to be comparable between participants. We also defined temporal criteria associated with time-related outcomes: (1) TTR, (2) slope of viral rebound, (3) time to peak VL, (4) time to setpoint, (5) time to different VL thresholds (ie, 200, 1000, 10 000, and

100 000 copies/mL). See [Table 1](#) and [Figure 2A](#) for a full definition of these criteria.

Identification of the Optimal Virological Criterion to Be Used as a Primary Endpoint

We sought to identify the optimal criterion summarizing viral dynamics that could be used as a proxy for the setpoint, meaning highly associated with the setpoint, and whose observation is less influenced by the duration of the ATI phase.

In each trial, placebo and intervention groups were pooled together to increase statistical power (see [Supplementary Materials Methods: Analysis of virological data at group level](#) for more explanation and analysis), and all analyses were performed at the trial level (ie, LIGHT/ILIADÉ/DALIA). First, a descriptive/comparative analysis of virological criteria was conducted to identify how they are affected by ATI designs. Second, Spearman correlations between criteria were evaluated and compared between trials to (1) determine how the ATI designs affect correlation patterns and (2) identify the criterion most strongly associated with the setpoint. Correlations between virological criteria and immunological features presented in [Supplementary Table 1](#) were also evaluated. See [Supplementary Materials Methods: Statistical analysis](#) for more details about statistical analysis.

Assessment of the Choice of Virological Restart ART Criteria on the Evaluation of the Virological Endpoint

To limit the risk for participants during the ATI phase, ART restart criteria are provided in protocols. These criteria describe conditions under which it is vital for a participant to restart ART before the end of the ATI phase. From ART restart, censoring of follow-up is considered due to strategy discontinuation and virological measurements are treated as missing for the evaluation of virological criteria. Although ART restart criteria can have a strong impact on virological endpoints, no real consensus has been reached about their definition [14]. In this work, we focused on virological ART restart criteria defined as the VL threshold above which participants have to resume ART—named, VL upper-threshold thereafter—and which induce the study of right-censored viral dynamics ([Figure 2B](#)).

We investigated the impact of VL upper-thresholds on the association between the setpoint and nAUC in the 3 trials. Three commonly considered VL upper-thresholds were investigated: 10 000, 50 000, and 100 000 copies/mL [10, 13, 19]. To this end, Spearman correlations were studied between the setpoint estimated on complete data and the nAUC calculated on right-censored viral dynamics, labeled right-censored nAUC ([Figure 2B](#)). Moreover, we investigated the need for a confirmation measure before any ART resumption. Therefore, correlations between the setpoint and the nAUC were evaluated considering censoring of follow-up once the VL upper-threshold has been exceeded either for (1) a single or (2) 2 consecutive viral measures.

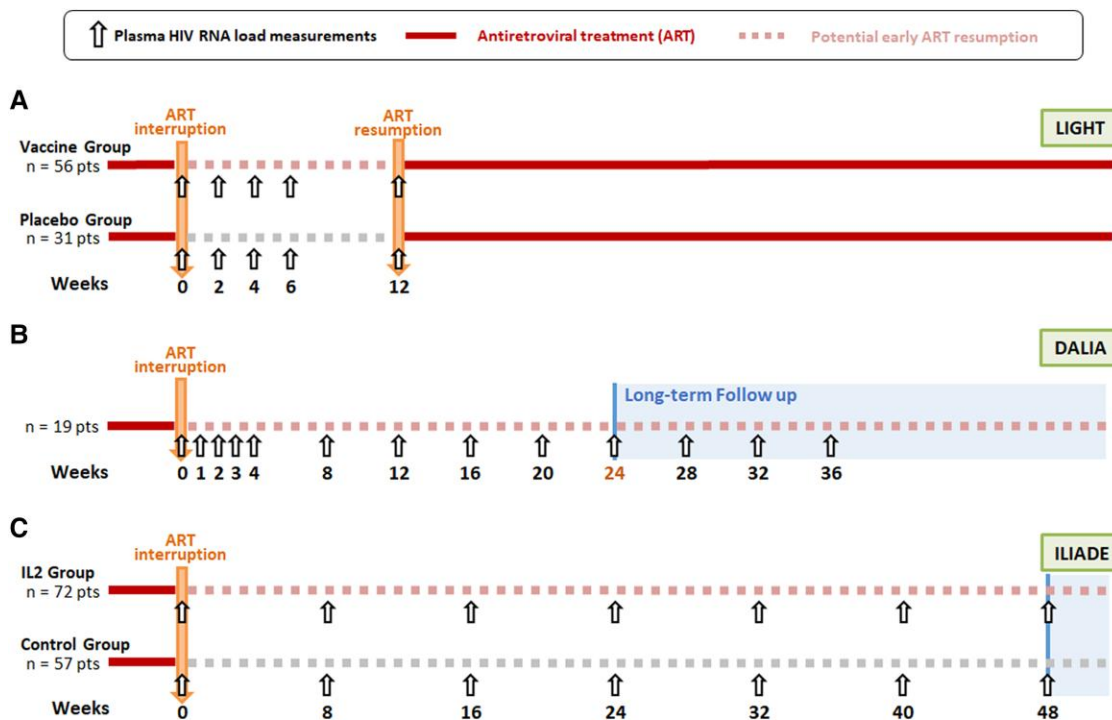


Figure 1. Study designs during the ATI phase of HIV therapeutic vaccine trials analyzed. *A*, LIGHT trial. At week 36 post-inclusion (labeled Week 0 here), the 87 participants (31 placebo and 56 vaccinated) interrupted ART for 12 weeks, with regular monitoring of immunological and virological measurements performed every 2 weeks. *B*, DALIA trial. At week 24 post-inclusion (labeled W0 post-ATI here), the 19 participants interrupted ART for a minimum of 24 weeks, with regular monitoring of immunological and virological measurements performed every 1 to 4 weeks. *C*, ILIADE trial. At week 24 post-inclusion (labeled W0 post-ATI here), the 129 participants (57 control and 72 treated) interrupted ART for 48 weeks, with monitoring of immunological and virological measurements every 8 weeks. (*A–C*) In the 3 trials, participants could prematurely restart ART during the protocol-defined ATI phase if they met the following criteria: (1) wish of participants or of their doctors, (2) CD4+ T-cell count dropped below 350 cells/ μ L at 2 consecutive measurements 2 weeks apart, and (3) occurrence of an opportunistic infection or a serious non-AIDS defining event. In DALIA, a drop of CD4+ T-cell count below 25% of total lymphocytes for 2 consecutive measurements was also considered. Analysis performed in this paper focused exclusively on viral load data collected during the ATI phase (ie, free-of-ART phase). In ILIADE and DALIA, only data collected from ART interruption to the time of primary endpoint (ie, at week 48 and week 24 post-ATI, respectively) were considered. Abbreviations: ART, antiretroviral treatment; ATI, analytical treatment interruption; HIV, human immunodeficiency virus; IL2, interleukin 2; pts, participants.

Table 1. Definitions of Virological Criteria Analyzed in the Study

Virological Criteria	Definition
VL magnitude-related criteria	
Peak VL (in \log_{10} copies/mL)	The maximum VL value during the ATI phase. In case of a long ATI phase (eg, in the ILIADE trial), an increasing viral dynamics can be observed in some patients after the stabilization of the dynamics and reach higher values than the peak of rebound. In that case, the higher VL value observed before the stabilization was kept.
Setpoint (in \log_{10} copies/mL)	The mean value of VL values belonging to the first sliding window with a height of 0.5 \log_{10} copies/mL, and with a width of at least 4 wk including at least 2 consecutive VL values [13].
Time-averaged AUC (nAUC) (in \log_{10} copies/mL)	Area under the viral rebound curve averaged by the duration (in weeks) of the ATI phase.
Temporal criteria	
Time to rebound (TTR) (in weeks)	The time between ART interruption and the first detectable VL value (>40 copies/mL in LIGHT and >50 copies/mL in ILIADE and DALIA).
Slope of viral rebound (in \log_{10} copies/mL/wk)	The slope from the last undetectable VL value to the peak VL.
Time to peak VL (in weeks)	The time between ART interruption and the peak VL (only for patients with observed peak VL).
Time to setpoint (in weeks)	The time between ART interruption and the first VL value belonging to the window defining the setpoint (only for patients with an observed setpoint).
Time to VL threshold (in weeks)	The time between ART interruption and the first VL value exceeding a specific VL threshold. Four different VL thresholds, previously used to analyze viral rebound, were considered: 200, 1000, 10 000, and 100 000 copies/mL [9, 15, 29].

Abbreviations: ART, antiretroviral treatment; ATI, analytical treatment interruption; VL, viral load.

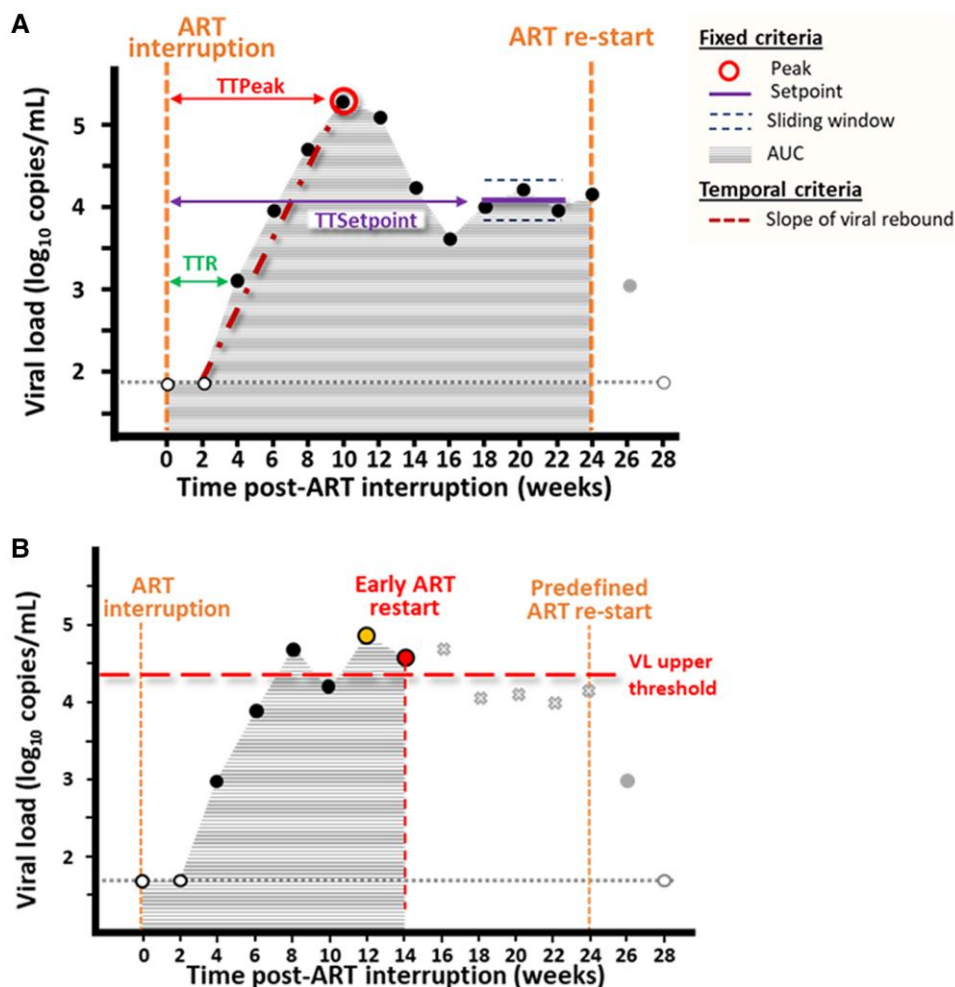


Figure 2. Graphical representation of virological criteria analyzed in the study. Black and white dots represent detectable and undetectable VL measurements collected during the ATI phase, respectively, and gray dots represent those collected after ART restart. The horizontal gray dotted line represents the limit of detection. *A*, Virological criteria describing viral rebound dynamics. *B*, Virological ART restart criteria inducing strategy discontinuation and censoring of follow-up. The orange dot shows the first VL measure exceeding the VL upper-threshold represented by the horizontal red dashed line (ie, time at which viral dynamic is censored when no confirmation measure is considered before ART restart). The red dot shows the VL measure at which the viral dynamic is censored when a confirmation measure is required before any ART resumption. Gray crosses display viral load measures unobserved due to censoring of follow-up after strategy discontinuation. Abbreviations: ART, antiretroviral treatment; ATI, analytical treatment interruption; AUC, area under the curve; TTPeak, time to VL peak; TTR, time to rebound; TTsetpoint, time to setpoint; VL, viral load.

RESULTS

Population

A total of 235 participants were included in the study: 87 in LIGHT, 129 in ILIADE, and 19 in DALIA (Figure 1 and Supplementary Materials Results: Population). Baseline characteristics of participants presented in Supplementary Table 1 pointed out the homogeneity of profiles in the 3 trials.

Assessment of Virological Criteria

Viral Rebound Dynamics. Viral rebound dynamics observed in the 3 trials are shown in Figure 3. The median length of follow-up before ART restart ranged from 12 to 48 weeks, with a median number of VL measurements during the ATI phase of 6 to 11 (Table 2). The percentages of participants prematurely

reinitiating their ART before the end of the ATI phase were equal to 21%, 26%, and 16% in LIGHT, ILIADE, and DALIA, respectively. Furthermore, except for a lower earliest VL dynamics in DALIA than in LIGHT, similar mean viral dynamics were observed in the 3 trials (see Supplementary Figure 3 and Supplementary Materials Results: Description of viral rebound dynamics and virological criteria). The virological criteria describing viral rebound dynamics in the different trials are summarized in Table 3 and Figure 4.

Viral Load Magnitude-Dependent Criteria. No statistical differences in setpoints were observed between trials with mean values ranging from 4.23 in DALIA to 4.42 \log_{10} copies/mL in LIGHT ($P = .39$) (Figure 4A). This result was consistent with

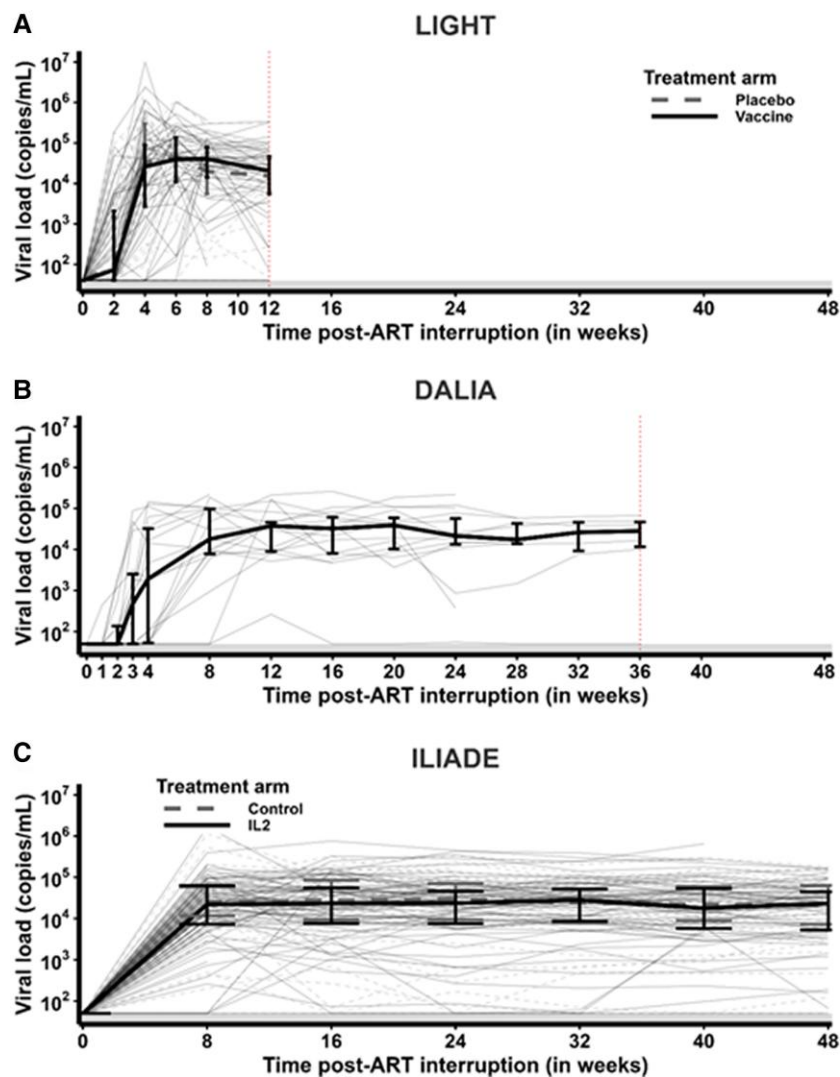


Figure 3. Viral dynamics observed in the 3 trials in the ATI phase. *A*, Viral dynamics observed during the 12-week ATI phase in the LIGHT trial, with monitoring every 2 weeks. *B*, Viral dynamics observed during the 36-week ATI period in the DALIA trial, with monitoring every 1 to 4 weeks. *C*, Viral dynamics observed during the 48-week ATI period in the ILIADE trial, with monitoring every 8 weeks. (*A–C*) Thick and thin lines represent the median and individual dynamics, respectively, and error bars represent interquartile ranges. Solid and dashed lines correspond to dynamics in therapeutic and control/placebo groups, respectively. Gray areas highlight limits of detection (ie, 40 copies/mL for LIGHT, and 50 copies/mL for ILIADE and DALIA). Red dotted vertical lines represent the end of ATI phase (week 12 in LIGHT and week 36 in DALIA). Abbreviations: ART, antiretroviral treatment; ATI, analytical treatment interruption; IL2, interleukin 2.

Table 2. Description of Analytical Treatment Interruption in the 3 HIV Clinical Trials

	LIGHT (n = 87)		ILIADE (n = 129)		DALIA (n = 19)
	Placebo (n = 31)	Vaccine (n = 56)	Control (n = 57)	IL-2 (n = 72)	
ATI duration, wk	12 [4; 12]	12 [2; 12]	48 [0; 48]	48 [0; 48]	28 [8; 36]
Median [min; max]					
No. of VL measurements during ATI	6 [3; 6]	6 [2; 6]	7 [1; 7]	7 [2; 7]	11 [6; 13]
Median [min; max]					
Premature ART restart, ^a n (%)	7 (23)	11 (20)	20 (35)	14 (19)	3 (16)

Abbreviations: ART, antiretroviral treatment; ATI, analytical treatment interruption; HIV, human immunodeficiency virus; IL-2, interleukin 2; max, maximum; min, minimum; VL, viral load.

^aEvaluation of the number and the percentage of patients who restart their ART before the end of the ATI phase, ie, before predefined ATI duration in LIGHT (12th week) or before time of the primary endpoint in ILIADE (48th week) and DALIA (24th week).

Table 3. Distribution of the Different Virological Criteria Estimated in the 3 HIV Clinical Trials

	LIGHT (N = 87)	ILIADE (N = 129)	DALIA (N = 19)	P ^a
VL magnitude-related criteria				
Peak VL, n (%) ^b	87 (100)	127 (98)	19 (100)	.002
Median [IQR]	4.92 [4.61; 5.42]	4.64 [4.23; 5.01]	4.94 [4.10; 5.18]	
Mean	4.84	4.55	4.58	
Setpoint, n (%) ^b	47 (54)	111 (86)	18 (95)	.39
Median [IQR]	4.53 [4.13; 4.92]	4.43 [3.99; 4.74]	4.15 [3.92; 4.74]	
Mean	4.42	4.27	4.23	
nAUC, n (%) ^b	87 (100)	127 (98)	19 (100)	.007
Median [IQR]	3.73 [3.27; 4.19]	4.14 [3.66; 4.41]	4.00 [3.68; 4.29]	
Mean	3.63	3.93	3.89	
Time-related criteria				
Time to rebound, n (%) ^c	83 (95)	125 (97)	19 (100)	<.0001
Median [IQR]	2 [2; 4]	8 [8; 8]	3 [2; 6]	
Mean	3.04	8.64	4.47	
Slope rebound, n (%) ^d	83 (95)	125 (97)	19 (100)	<.0001
Median [IQR]	0.75 [0.57; 1.06]	0.28 [0.17; 0.36]	0.52 [0.36; 0.89]	
Mean	0.87	0.27	0.70	
Time to peak VL, n (%) ^c	87 (100)	126 (98)	19 (100)	<.0001
Median [IQR]	6 [4; 6]	8 [8; 16]	8 [4; 12]	
Mean	5.77	13.84	8.26	
Time to setpoint, n (%) ^c	47 (54)	111 (86)	18 (95)	<.0001
Median [IQR]	6 [6; 8]	16 [8; 24]	10 [8; 15]	
Mean	6.43	15.86	10.89	
Time to 200 copies/mL, n (%) ^c	82 (94)	126 (98)	19 (100)	<.0001
Median [IQR]	4 [2; 4]	8 [8; 8]	3 [3; 8]	
Mean	3.46	8.83	5.32	
Time to 1000 copies/mL, n (%) ^c	80 (92)	121 (94)	18 (95)	<.0001
Median [IQR]	4 [2; 4]	8 [8; 8]	4 [3; 8]	
Mean	3.78	8.93	5.39	
Time to 10 000 copies/mL, n (%) ^c	78 (90)	107 (83)	18 (95)	<.0001
Median [IQR]	4 [4; 6]	8 [8; 8]	8 [4; 12]	
Mean	4.79	9.94	9.11	
Time to 100 000 copies/mL, n (%) ^c	42 (48)	39 (30)	10 (53)	<.0001
Median [IQR]	4 [4; 6]	16 [8; 16]	8 [5; 12]	
Mean	5.10	17.23	8.80	

"N" indicates the total number of participants in the trial, "n" indicates the number of participants with observed endpoints in each trial.

Abbreviations: ATI, analytical treatment interruption; HIV, human immunodeficiency virus; IQR, interquartile range; nAUC, time-averaged area under the curve; VL, viral load.

^aP values of the multiple-group comparisons (Kruskal–Wallis test).

^blog₁₀ copies/mL.

^cWeeks.

^dlog₁₀ copies/mL/week.

the absence of significant differences of VL dynamics beyond week 4. However, a lower percentage of participants reached the setpoint in LIGHT (54%) compared with DALIA (95%) and ILIADE (86%) because of its shorter 12-week ATI phase, making its observation more difficult.

Both the peak VL and the nAUC were significantly different between LIGHT and ILIADE, whereas no differences were observed between DALIA and LIGHT, or DALIA and ILIADE. As shown in [Figure 4B](#) and [4C](#), the mean peak VL was significantly higher in LIGHT than in ILIADE (+6%, $P < .001$), while the nAUC was significantly lower (−8%, $P < .01$). Although not a direct time-dependent criterion, the study design can explain the lower peak in ILIADE: the lower the sampling frequency

(a measure every 8 weeks in ILIADE instead of 2 weeks in LIGHT), the higher the probability to miss the peak (see [Supplementary Figure 4](#) for an illustration).

Time-Dependent Criteria. The time-dependent criteria showed strong dependencies on the study designs—that is, the ATI duration and sampling frequency. As shown in [Table 3](#) and [Figure 4D](#) and [4F](#), with VL measurements collected every 8 weeks, significantly different results were found in ILIADE than in LIGHT and DALIA. Specifically, we found a higher mean TTR and time to setpoint (TTR: 8.64 vs 3.04 and 4.47 weeks, respectively; $P < .001$; time to setpoint: 15.9 vs 6.43 and 10.9 weeks, respectively; $P < .001$). In contrast, a

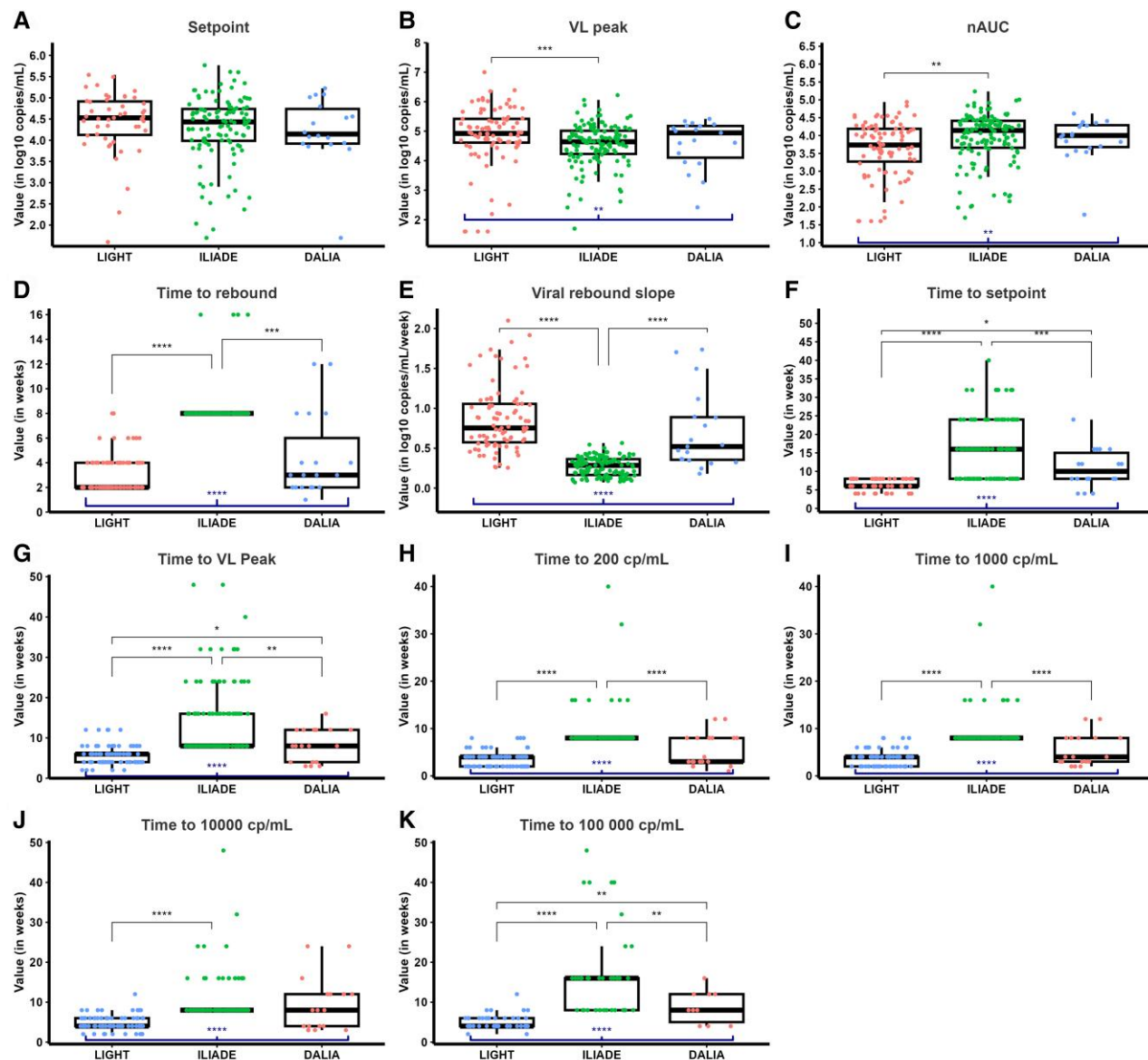


Figure 4. Distribution of different virological criteria within each trial. Blue thick brackets below boxplots and black thin brackets above boxplots show significant P values of the multiple-group comparisons (Kruskal–Wallis test) and pairwise comparisons (Mann–Whitney U test), respectively. Significant P values after multiplicity adjustment: * $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$, **** $P \leq .0001$. A, Distribution of the setpoint, in \log_{10} copies/mL. B, Distribution of the peak VL, in \log_{10} copies/mL. C, Distribution of the nAUC, in \log_{10} copies/mL. D, Distribution of the time to rebound, in weeks. E, Distribution of the slope of the viral rebound, in \log_{10} copies/mL/wk. F, Distribution of the time to setpoint, in weeks. G, Distribution of the time to peak VL, in weeks. H, Time to 200 copies/mL of VL, in weeks. I, Time to 1000 copies/mL of VL, in weeks. J, Time to 10 000 copies/mL of VL, in weeks. K, Time to 100 000 copies/mL of VL, in weeks. Abbreviations: cp, copies; nAUC, time-averaged area under the curve; VL, viral load.

significantly lower slope of rebound was observed in ILIADE than in LIGHT and DALIA (-69% and -62% , respectively; $P < .0001$), which mostly results from the higher TTR. Finally, similar temporal endpoints were observed in LIGHT and DALIA.

Analysis of Correlations Between Virological Criteria

To identify virological criteria highly associated with the setpoint, we performed a correlation analysis. Figure 5 displays Spearman

correlations between the 5 criteria most frequently used (see Supplementary Figure 5 for results of the 11 criteria, and Supplementary Figure 6 for scatterplots). Similar patterns of correlations were obtained in the 3 trials. First, there was an absence of correlations between the TTR and the setpoint, the 2 virological endpoints recommended to assess vaccine efficacy in ATI trials [10]. Second, we identified strong significant positive correlations between the setpoint and both the peak VL and the nAUC ($P < .001$), with stronger correlations for the nAUC

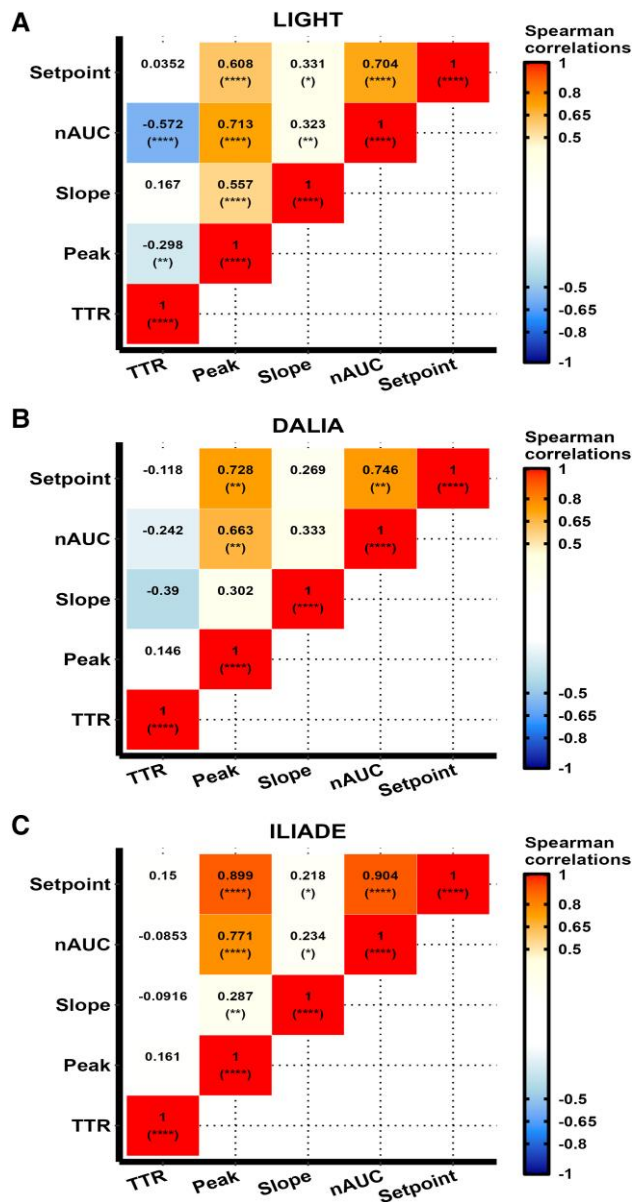


Figure 5. Heatmap of pairwise Spearman correlations between the 5 main virological criteria in the 3 clinical studies. *A*, LIGHT clinical trial ($n = 87$). *B*, DALIA clinical trial ($n = 19$). *C*, ILIADE clinical trial ($n = 129$). (*A–C*) Correlations higher than 0.5 are colored in orange-red palette and correlations lower than -0.5 in blue palette. P values adjusted for multiplicity testing are indicated in brackets: * $P \leq .05$, ** $P \leq .01$, *** $P \leq .001$, **** $P \leq .0001$. Abbreviations: nAUC, time-averaged area under the curve; TTR, time to rebound.

(0.70/0.61 in LIGHT, 0.90 for both in ILIADE, and 0.75/0.73 in DALIA). The correlations between the TTR and other endpoints were less consistent across trials. For instance, a negative correlation between the TTR and the nAUC was only found in LIGHT (-0.57 ; $P < .0001$). Correlation analysis performed on pre-ATI immunological features revealed the absence of association between the setpoint and the immunological measurements.

These results identified the nAUC as the virological criterion most strongly correlated with the setpoint, and which can be evaluated regardless of the design of the ATI phase.

Virological Restart Criteria Impact the Association Between the Setpoint and the nAUC

We assessed the impact of VL-based ART restart criteria (Figure 2B) on the correlation between the setpoint and the nAUC. Figure 6 illustrates the Spearman correlations between the setpoint and the right-censored nAUC for different VL upper-thresholds, with or without a confirmation measure before ART restart. In most cases, the higher the VL upper-threshold, the more significant and stronger the correlation coefficient. Moreover, results in LIGHT and DALIA highlighted the benefit of a confirmation measure to retrieve significant correlations. While no correlations were identified in the absence of a confirmation measure, positive significant correlations were identified when censoring occurred after 2 consecutive measures above 100 000 copies/mL. The use of a low threshold to censor data can lead to nonconclusive results (nonsignificant correlations), or even to wrong conclusions about vaccine efficacy. Indeed, an inversion of the sign of correlations was observed without a confirmation measure in DALIA and LIGHT around 10 000 copies/mL. A VL upper-threshold of 100 000 copies/mL for 2 consecutive measures allowed to retrieve more than 50% of the magnitude of the correlation between the setpoint and nAUC (LIGHT: 50%; ILIADE: 94%; DALIA: 83%).

DISCUSSION

Key Recommendations for Future Studies Assessing Efficacy of HIV Strategies to Control Viral Replication Without ART

The present study validated, on real data, recommendations made by the consensus meeting [10]:

1. Time-averaged AUC during the ATI phase, as a proxy to the setpoint, can be used as the primary endpoint
2. The optimal design of the ATI phase minimizing the risk for participants and maximizing the evaluation of treatment efficacy includes:
 - (a) A duration of 12 to 24 weeks
 - (b) Weekly VL monitoring for 12 weeks, and every 2–4 weeks thereafter
3. ART should not be restarted before a confirmed VL of more than 100 000 copies/mL if the safety of the patient is guaranteed

This analysis highlights the necessity to accurately design the ATI phase and choose the optimal virological endpoint and VL-based ART restart criteria in line with the aim of the study. Moreover, the nAUC was identified as the virological criterion most strongly correlated with the setpoint. As expected, we

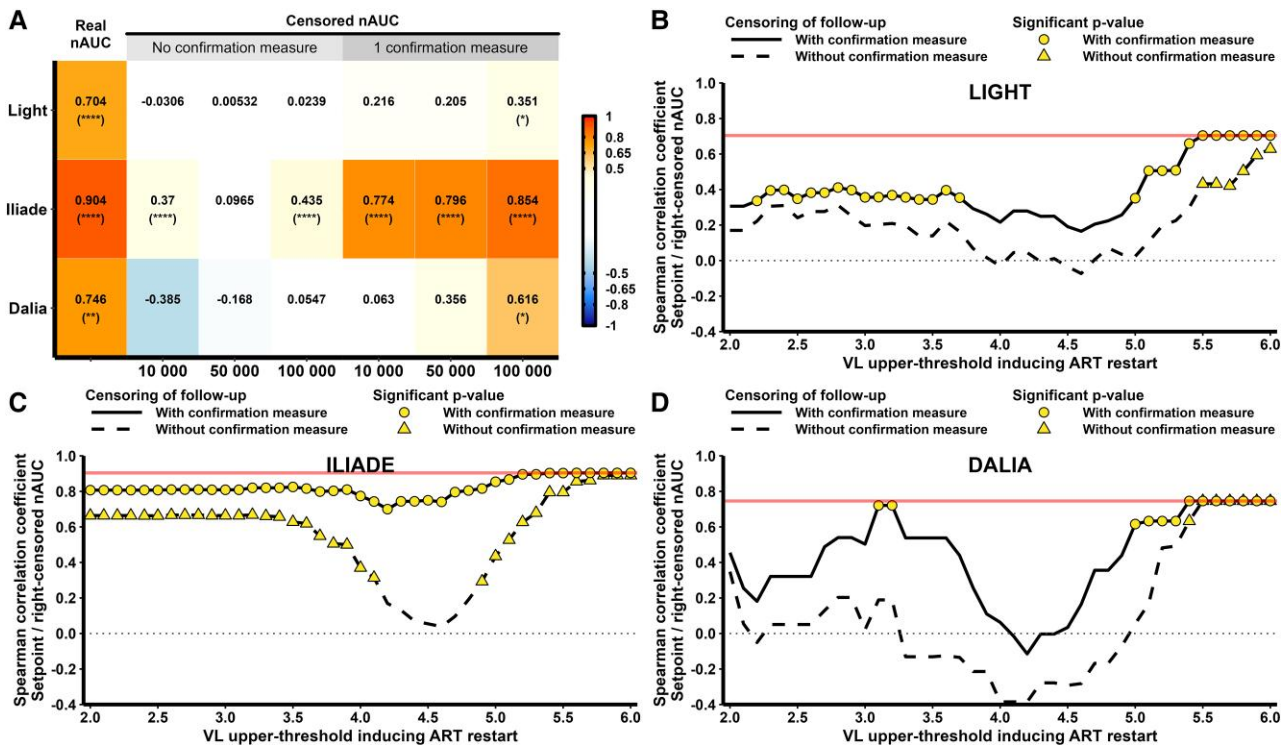


Figure 6. Spearman correlations between the setpoint and nAUC calculated on right-censored viral dynamics according to VL upper-thresholds. *A*, Heatmap of Spearman correlations in each trial (*y*-axis) between the setpoint and nAUC, whether with or without censoring of follow-up, and with or without consideration of a confirmation measure before premature ART restart. Three commonly used VL upper-thresholds are considered: 10 000 copies/mL, 50 000 copies/mL, and 100 000 copies/mL. Significant positive and negative correlations are highlighted in red and blue, respectively. (*B–D*) Analysis of Spearman correlations between the setpoint estimated on complete virological data, and the nAUC estimated on right-censored viral dynamics. The *x*-axis represents the VL upper-thresholds above which censoring of follow-up was considered. The *y*-axis represents the value of the correlation coefficient between the setpoint and the right-censored nAUC. Solid and dashed lines represent the results with or without a confirmation measure in the calculation of the right-censored nAUC, respectively. Yellow symbols (circles and triangles for with or without confirmation, respectively) highlight significant correlations (adjusted $P \leq .05$). The horizontal gray dotted line represents the transition between positive and negative correlations. The horizontal red solid line represents the value of the correlation coefficient between the setpoint and the nAUC estimated on complete data. (*B*) LIGHT trial. (*C*) ILIADE trial. (*D*) DALIA trial. Abbreviations: ART, antiretroviral treatment; nAUC, time-averaged area under the curve; VL, viral load.

found that especially the time-dependent virological criteria varied depending on the design of the ATI phase. In agreement with previous ATI studies [30, 31], participants reached a stable viral setpoint during the ATI phase after 8–12 weeks off-ART, confirming the use of an ATI phase of more than 12 weeks. While HIV research is moving towards short ATI phases with a lower risk of uncontrolled viremia [20], studies looking for post-treatment controllers [19, 21] showed the benefits of more permissive protocols to identify this population that experienced viral replication before controlling. Similar to this study, we showed that using an overly conservative threshold for a virological ART restart criterion can increase the risk of missing important effects of immune intervention on viral control. On the contrary, the use of a high value reinforces the nAUC as a valid proxy to the setpoint, and we showed that the nAUC remains a valuable endpoint even in the case of censored follow-up [32]. Although no virological ART restart criteria were considered in the 3 trials, 23% of participants prematurely restart ART. Since the observation of the setpoint is strongly dependent on

the study design, the choice of the virological ART restart criterion has a direct effect on the statistical power to assess the treatment efficacy. The sample size should therefore be carefully evaluated. In contrast, unlike the setpoint, the nAUC can be observed regardless of the design of the ATI phase, making the sample size less dependent on the stringency protocols. Nevertheless, the nAUC is highly dependent on (1) the duration of the ATI phase, as the shorter the ATI, the less it is representative of the setpoint, and the longer the ATI, the less it depends on the early phase of viral rebound, and (2) the sampling frequency, as the accuracy of the calculation increases with it. Our results of correlations between virological criteria were consistent with those reported in other trials [13]. The absence of correlation between time to rebound and setpoint has already been reported in other studies [15], and emphasizes the need to choose the most accurate primary endpoint for the aim of the study. Biologically, this could be explained by the fact that the initiation of viral replication and the subsequent control are driven by different biological mechanisms. A recall T-cell

response stimulated by the start of viral replication is potentially responsible for post-replication control [29, 33]. Hence, the pre-ART VL is more correlated to viral setpoint [15] rather than TTR. In the present work, it is also interesting to point out that the viral slope is weakly correlated with the viral setpoint, suggesting that the secondary immune response is playing a bigger role in controlling viral replication after the peak than what is observed during the primary infection.

This study is based on 3 clinical trials and thus the generalizability of our results may be limited. However, the information brought by real observed data helps to go beyond simulations [12]. When the intervention and its expected impact are based on mechanisms other than active immune control of viral replication, such as passive immunization through neutralizing antibodies [34], other endpoints and designs should be considered.

Beyond statistical and clinical considerations, participants' perceptions should be taken into account and recent studies have shown the good acceptability of ATI trials [8, 9, 35] as long as severe side effects are avoided [36]. According to these studies, some respondents would not accept persistent viremia (35% in Lau et al [37]). This would potentially restrict the inclusion rate in the trials. Also, the preferred frequency of biological measurements and clinical monitoring during ATI was monthly [37]. Biotechnological improvements that make measurements at home feasible could help cope with these participants' preference [38].

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

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Author contributions. Y. L., M. P., and R. T. conceptualized the study. M. A. accessed and verified data and conducted the formal analysis. M. P. and R. T. supervised the analysis. M. A. created the first draft of the figures, and M. A. and R. T. wrote the first draft of the manuscript. All authors contributed to data interpretation. All authors critically revised and edited the manuscript and approved the final version for submission.

Data availability. The data that support the findings of this study are available from the corresponding author, R. T., upon reasonable request.

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CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS⁴⁻⁹

Treatment-naïve resistance rates, with up to **3 years of evidence**⁵⁻⁷

0%
(n=0/1,885)^{*4}
REAL-WORLD EVIDENCE

0.1%
(n=1/953)^{**1,11,5,5-7}
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**¹⁻³

0.03%
(n=10/35,888)^{*4}
REAL-WORLD EVIDENCE

0%
(n=0/615)^{11,5,8,9}
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY¹⁰

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:^{4-9,11,12}



NO PRIOR TREATMENT EXPERIENCE¹³



NO BASELINE RESISTANCE TESTING¹³

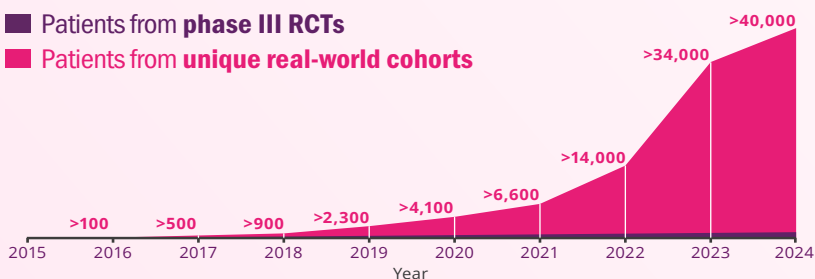


HIGH BASELINE VIRAL LOAD
(>100,000 copies/mL and even >1M copies/mL)^{6,13}



LOW CD4 + COUNT
(≤200 cells/mm³)¹³

■ Patients from phase III RCTs
■ Patients from unique real-world cohorts



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

LEARN MORE 

DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.¹³

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

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ABBREVIATIONS

3TC, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).⁵⁻⁷

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).¹³

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.⁶

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.⁷ Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).^{8,9}

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).^{8,13}

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).⁹