nature communications

Article

https://doi.org/10.1038/s41467-025-56116-1

Time to HIV viral rebound and frequency of post-treatment control after analytical interruption of antiretroviral therapy: an individual data-based meta-analysis of 24 prospective studies

Received: 29 October 2024

Accepted: 8 January 2025

Published online: 21 January 2025

Check for updates

A list of authors and their affiliations appears at the end of the paper

The only current strategy to test efficacy of novel interventions for sustained HIV control without antiretroviral therapy (ART) among people with HIV (PWH) is through an analytical treatment interruption (ATI). Inclusion of 'placebo' controls in ATIs poses ethical, logistical, and economic challenges. To understand viral dynamics and rates of post-treatment control (PTC) after ATI among PWH receiving either placebo or no intervention, we undertook an individual-participant data meta-analysis. In total, 24 eligible prospective studies with 382 individuals with ≥5 plasma HIV RNA viral loads (pVLs) within the first 84 days post-ATI were included. Early-ART was defined as ART initiation within 6 months of HIV acquisition; others were classified as late-ART or unknown. Median age was 42 years, 91% male, 75% white, 45% received early-ART. Median time to pVL >50, >400, and >10,000 copies/mL was 16 days (interquartile range [IQR]:13–25), 21 (IQR:15–28), and 32 (IQR:20–35), respectively. PTC defined as pVL <50 copies/mL at day 84 occurred in 4% ($n = 14$) of participants (6% early-ART and 1% late-ART). Sustained PTC of pVL <50 copies/ml after 84 days is rare in PWH, especially in those starting ART late. Our findings inform future interventional HIV cure/remission trials on study size and design.

Antiretroviral therapy (ART) has dramatically improved survival and quality of life for people living with human immunodeficiency virus type 1 (HIV)[1]. National and international guidelines recommend lifelong ART initiated at the time of diagnosis[1–3]. Adherence to ART leads to viral suppression, prevents HIV disease progression, and eliminates the risk of onward viral transmission[1]. However, ART carries risks of toxicities and side effects, requiring sustaining lifelong adherence. Access to medication burdens people with HIV (PWH) and healthcare systems, particularly in settings with limited resources and populations with high HIV prevalence[4]. There is widespread interest in exploring alternative approaches to achieve long-term ART-free virological control.

ART, whilst effectively blocking viral replication, is unable to eradicate HIV due to the persistence of a reservoir of latently infected cells[5], which is the source of viral recrudescence when ART is stopped. While there has been much advance in assays evaluating the HIV reservoir and HIV-specific immunity, none can accurately predict which individuals will achieve post-treatment control (PTC) after stopping ART[6]. Hence, to measure clinical efficacy of any experimental approach towards eliminating the HIV reservoir or inducing immune-

e-mail: jesper@gunst.dk

mediated suppression of virus replication, ART must be carefully interrupted in a controlled setting; so-called analytical treatment interruption (ATI)[7–11]. A collaborative group met to develop guidelines on how to safely undertake ATI trials[12] frequently monitored plasma HIV RNA viral load (pVL) and CD4 + T cell counts throughout the period of ATI[10,11,13–15] but these recommendations are based on observations from multiple different studies, many of which were carried out using different ATI protocols and older ART regimens[10]. The only known potential determinant of PTC from previous analyses is time from HIV acquisition to ART initiation[10]; while generally, measures of the HIV reservoir do not accurately predict PTC[13–16].

Although some individuals have demonstrated PTC after ATI[10] for the majority of PWH, viral rebound occurs rapidly, usually within weeks after stopping ART[7,8,17–19]. Such ATI protocols are intense and benefit greatly from altruism and commitment from the community of PWH to reach efficacy outcomes[20,21]. While inclusion of placebo or no-intervention groups to study design add great value scientifically, and may be necessary in early phase trials, ATI carries potential risk to participants and their partners[22,23].

To comprehensively map patterns of virological rebound after stopping ART under close monitoring and to inform future study designs, we undertook an individual participant data meta-analysis from studies that included an ATI among individuals that received placebo or "no intervention" prior to stopping ART. We further sought to identify pre-ATI clinical factors that influenced the timing of viral rebound.

Results

In total, 942 publications were identified and screened under the search terms (Fig. 1). Of these studies 164 were ATI studies, and out of these 24 studies[14,17,24–43] were included in this individual data-based meta-analysis, and 142 ATI studies were excluded due to different reason (Fig. 1). Table 1 summarises the studies included in this analysis.

Characteristics of included studies

Of the 24 studies included in our analysis, 22 were published in peer reviewed journals between 2000-2024[14,17,24–43] and 2 studies have yet to be published (AELIX-003 [NCT04364035] and BNC03 [NCT05208125]). Fourteen were RCTs ([17,25,26,28,31,32,35,37,39–41,44] + AELIX-003 and BNC03) and ten were single-arm ATI studies[14,24,29,30,33,34,36,38,42,43]. Thirteen studies were undertaken in Northern Europe ([14,17,31–34,38–40,42,43] + AELIX-003 and BNC03) and eleven studies in North America[24–30,35–37,41]. Most studies had only

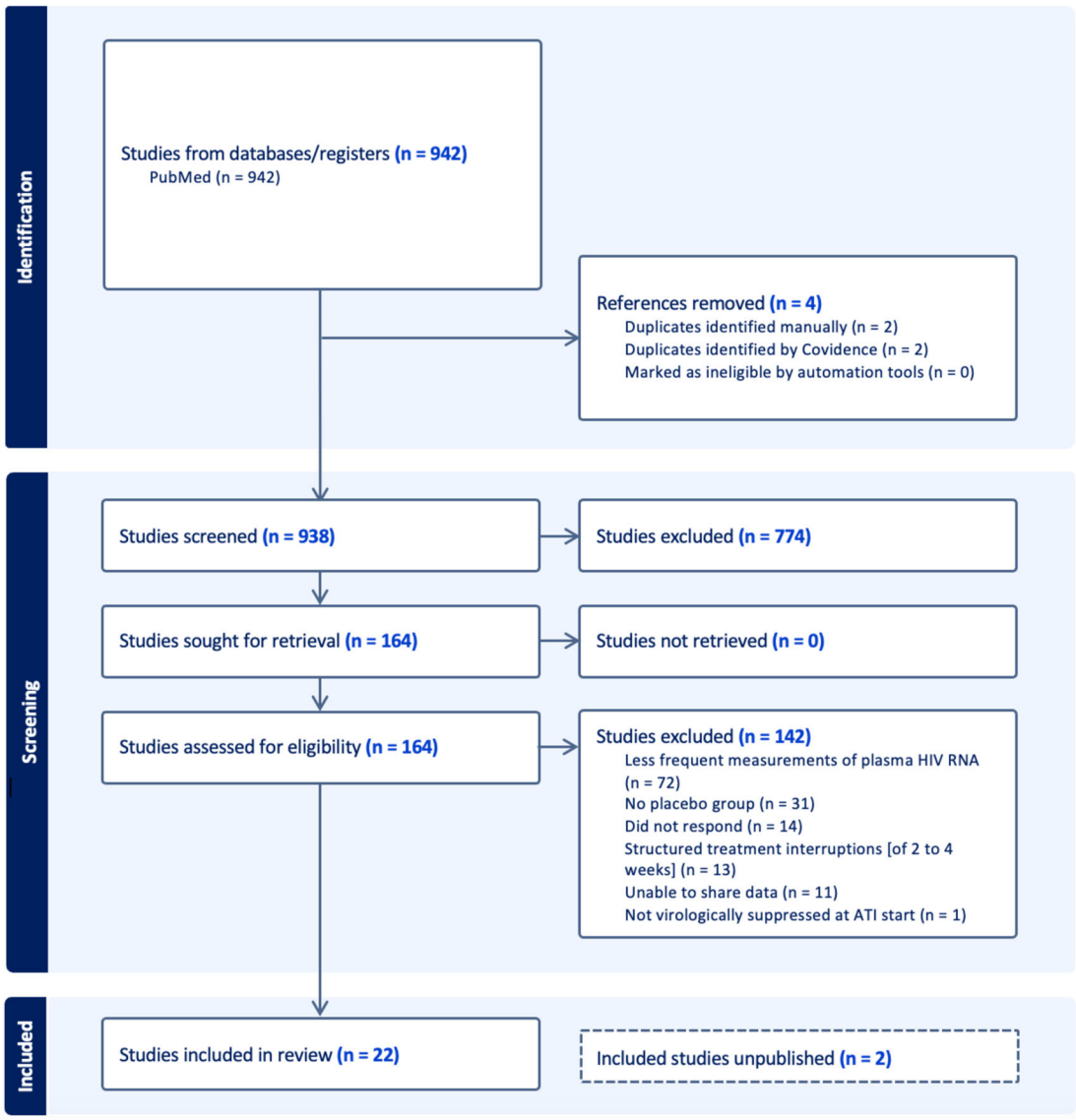


Fig. 1 | Flowchart of literature review.

https://doi.org/10.1038/s41467-025-56116-1

Table 1 | ATI studies and individuals in the meta-analysis

Author, year	*n*	Male, *n* (%)	Age	Race and ethnicity, %				PreART					At ATI start					During ATI		
								Plasma HIV RNA [copies/mL]	Nadir CD4 + T cell count [per mm^3]	Stage at ART initiation, %			CD4 + T cell count	ART regimen, %				Time to viremia [copies/mL], days[b]		
				Asian	Black	White	Other			Early	Chronic	Unknown	[per mm3]	INSTI-based	NNRTI-based	PI-based	Other	>50	>400	>10,000
Ruiz [34]	12	3 (25)	34 (29;38)	0	0	100	0	32,520 (25,260; 65,826)	NA	0	100	0	1250 (996; 1533)	0	0	100	0	14 (11;20)	19 (13;25)	NA
Papasavvas [41]	13[a]	10 (77)	41 (23;49)	0	54	38	8	NA	311 (30; 534)	0	46	54	720 (307; 1320)	0	77	23	0	28 (15;34)	28 (27;35)	28 (28;41)
Jacobson [27]	19	18 (95)	46 (42;51)	0	11	84	5	NA	NA	0	100	0	836 (657; 909)	0	79	21	0	24 (14;31)	26 (20;33)	34 (26;40)
Kilby [28]	12	11 (92)	42 (35;43)	8	17	50	25	NA	NA	0	100	0	681 (599; 781)	0	67	33	0	16 (14;27)	21 (17;31)	29 (23;35)
Volberding [29]	67[a]	63 (94)	37 (28;41)	1	7	75	16	NA	NA	100	0	0	844 (715; 1066)	0	0	100	0	14 (12;20)	20 (14;26)	27 (20;38)
Rosenberg [26]	8[a]	8 (100)	42 (34;45)	0	0	75	25	NA	NA	100	0	0	1060 (685; 1125)	0	50	50	0	31 (28;38)	38 (29;43)	NA
Schooley [25]	27[a]	27 (100)	43 (40;48)	4	11	78	7	NA	NA	0	100	0	807 (749; 1090)	0	63	37	0	17 (13;35)	25 (17;35)	34 (21;39)
Rothenberger [24]	14	13 (93)	47 (43;49)	0	29	71	0	NA	201 (180; 369)	0	100	0	499 (388; 670)	21	0	79	0	14 (10;18)	16 (13;19)	NA
Calin [33]	10	7 (70)	42 (37;47)	0	10	90	0	10,871 (4157; 22,790)	495 (369; 571)	0	40	60	1046 (862; 1299)	30	10	30	30	28 (14;28)	28 (28;29)	NA
Sneller [35]	15	15 (100)	43 (33;48)	13	13	67	1	51,185 (13,352; 185,983)	697 (448; 763)	100	0	0	679 (522; 909)	93	0	7	0	28 (28;30)	29 (28;42)	55 (40;55)
Castagna [14]	8[a]	7 (88)	50 (48;53)	0	13	88	0	30,190 (8145; 57,500)	353 (255; 391)	0	100	0	765 (685; 989)	25	38	38	0	18 (14;25)	18 (14;29)	24 (15;28)
de Jong [31]	8	8 (100)	40 (35;53)	NA				84,750 (19,505; 116,850)	420 (372;489)	75	25	0	402 (373; 455)	100	0	0	0	15 (14;28)	21 (14;28)	28 (27;48)
De Scheerder [38]	11	10 (91)	40 (38;47)	0	0	100	0	64,583 (47,460; 115,752)	389 (335; 417)	36	64	0	688 (617; 872)	100	0	0	0	17 (16;27)	20 (18;27)	NA
Pannus [42]	15[a]	14 (93)	42 (38;54)	0	0	100	0	NA	446 (342; 501)	67	33	0	710 (610; 986)	53	40	7	0	28 (14;41)	32 (27;41)	NA
Sneller [36]	22	20 (91)	51 (46;56)	0	41	45	14	46,519 (11,799; 82,127)	327 (240;454)	0	100	0	767 (594; 941)	95	5	0	0	16 (11;20)	20 (15;25)	24 (20;32)
Leal [40]	7	7 (100)	43 (41;48)	0	0	100	0	10,400 (8906; 52,850)	480 (460; 786)	0	100	0	744 (633; 1086)	100	0	0	0	14 (7;27)	27 (14;27)	28 (27;41)
Bailón [32]	14[a]	14 (100)	36 (32;43)	NA				82,595 (32,695; 608,290)	541 (453; 601)	100	0	0	830 (677; 1117)	100	0	0	0	17 (14;19)	20 (16;25)	31 (22;40)

https://doi.org/10.1038/s41467-025-56116-1

Table 1 (continued) | ATI studies and individuals in the meta-analysis

Author, year	*n*	Male, *n* (%)	Age	Race and ethnicity, %				PreART					At ATI start					During ATI		
								Plasma HIV RNA [copies/mL]	Nadir CD4 + T cell count [per mm^3]	Stage at ART initiation, %			CD4 + T cell count	ART regimen, %				Time to viremia [copies/mL], days[b]		
				Asian	Black	White	Other			Early	Chronic	Unknown	[per mm3]	INSTI-based	NNRTI-based	PI-based	Other	>50	>400	>10,000
Gunst [39]	4	2 (50)	41 (33;48)	25	50	25	0	23,650 (11,830; 51,350)	459 (377; 606)	75	25	0	859 (799; 888)	100	0	0	0	14 (14;14)	18 (14;25)	NA
Li [30]	45	42 (93)	45 (35;52)	13	9	56	22	44,504 (10,600; 255,175)	378 (324; 471)	27	73	0	720 (600; 938)	98	0	2	0	17 (14;27)	21 (18;27)	28 (21;33)
Sneller [37]	7	7 (100)	34 (33;47)	14	0	86	0	82,132 (36,856; 731,370)	330 (300; 491)	100	0	0	668 (604; 786)	100	0	0	0	23 (21;23)	23 (21;23)	23 (23;34)
Gunst [17]	10	9 (90)	52 (46;55)	0	0	100	0	NA	NA	0	70	30	692 (573; 750)	70	0	30	0	20 (15;21)	21 (20;26)	25 (20;50)
Tipoe [43]	7	7 (100)	41 (37;52)	0	0	100	0	1,000,000 (999,999; 1,155,656)	792 (715; 801)	100	0	0	NA	86	0	14	0	27 (15;41)	29 (17;40)	38 (33;42)
AELIX-003 (NCT04364035)[c]	17	17 (100)	39 (28;51)	0	0	94	6	82,000 (20,600; 806,000)	491 (447; 600)	100	0	0	850 (725; 1080)	94	0	0	6	20 (14;26)	20 (14;27)	27 (20;34)
BNC03 (NCT05208125)[c]	10	10 (100)	39 (36;50)	0	0	90	10	88,790 (10,346; 147,534)	484 (407; 579)	0	100	0	801 (669; 1018)	90	0	10	0	15 (14;33)	22 (15;40)	26 (20;29)
Total	382	349 (91)	42 (35;49)	4	12	75	10	48,400 (14,000; 150,000)	422 (330; 558)	45	51	4	781 (611; 1007)	48	17	34	1	18 (13;28)	22 (16;29)	34 (21;48)

Data are median (interquartile range) unless otherwise stated. Stage at ART initiation indicates either early-ART: within 6 months of HIV acquisition or late-ART: beyond 6 months of HIV acquisition.

ART antiretroviral therapy, *ATI* ART interruption, *PI* protease inhibitor, *INSTI* integrase strand transfer inhibitor, *NA* not available, *NNRTI* non-nucleoside reverse transcriptase inhibitor.

[a]Individuals excluded, whom did not fulfil the inclusion criteria of frequent measurements of plasma HIV RNA.

[b]Individuals can only contribute to data if still off ART and the threshold is meet.

[c]Studies not published.

small "placebo" participant numbers with the smallest involving 4 individuals[39] and the largest being 69 individuals[29]. Restart criteria for ART between the studies were based upon pVL levels and CD4 + T cell counts, but differed on the exact threshold (Supplementary Table S2).

Study participant demographics

The characteristics of the analysed ATI study participants are shown in Table 1. From the 382 participants of the 24 studies, 91% were male and 75% white. The median age was 42 (interquartile range [IQR] 35–49) years. The median CD4 + T cell count at ART initiation was 422 (330–558) per mm^3 and median pre-ART pVL was 48,400 (14,000–150,000) copies/mL. Forty-five and 51 percent of participants were categorized as early-ART and late-ART, respectively, while 4% were categorized as 'unknown'. At the start of ATI, the median CD4 + T cell count was 781 (IQR 611–1,007) per mm^3. Forty-eight percent were on an integrase-strand inhibitor regimen, while 17% were on a NNRTI-containing ART regimen at the time of ATI.

NNRTI impacts time to viremia

NNRTI has been shown to be associated with longer time to viral rebound likely reflecting an antiretroviral drug 'tail' into the ATI due to the long half-life of NNRTIs. In agreement with previous analyses, univariable analysis, non-NNRTI regimens compared to NNRTI regimens at ATI start were associated with shorter time to viremia (Supplementary Fig. S1a, b). In multivariable analysis, NNRTI regimen at ATI start continued to be associated with longer time to pVL >50 copies/mL (Supplementary Fig. S1a: HR 0.50, $P < 0.01$). However, due to the risk of ART drug resistance, current ATI trials no longer recommend NNRTI regimens and to make our observations pertinent to current recommendations individuals entering an ATI on NNRTI regimens were omitted from the analyses of time to viral rebound, although included in the overall analyses of PTC at day 84 of ATI.

Viral kinetics

While viral rebound kinetics following ART interruption differed (Fig. 2a), most individuals followed a similar pattern. Forty-four percent of the participants had a pVL below 50 copies/mL at day 14 after stopping ART but only 4% had a pVL below 50 copies/mL at day 84 (Fig. 2b).The median time to pVL >50 copies/mL after ART interruption was 16 days (IQR: 13–25), while time to pVL >400 and >10,000 copies/mL was 21 (IQR: 15–28) days and 32 (IQR: 20–35) days, respectively (Fig. 2c–e). Viral rebound kinetics among early-ART and late-ART individuals are shown in Supplementary Fig. S2 and time to viremia data for all individuals irrespective of ART regimen is shown in Supplementary Fig. S3.

Collectively, these data demonstrate that in more than 75% of individuals (not on NNRTI regimens), pVL rebounds within 21 days and only 14 (4%) people have suppressed viremia through day 84.

Post-treatment control

Out of the 14 PTCs with pVL below 50 copies/mL at day 84 (Fig. 3a), only 4 (29%) individuals had pVLs <50 copies/mL at all prior measurements. The other 10 individuals had variable levels of viremia prior to regaining viral control to <50 copies/mL, with 29% ($n = 4$) reaching a peak pVL 50–399 copies/mL, 29% ($n = 4$) with peak pVL between 400–10,000 copies/mL, and 14% ($n = 2$) reaching peak pVL above 10,000 copies/mL (Fig. 3b, c). Examining the total study cohort of 382 individuals, categorized by levels of peak pVL <50, 50–399, 400–10,000, and >10,000 copies/mL, the percentage of PTCs at day 84 within each category were 1%, 1%, 1% and 0.5%, respectively.

Among the 14 PTCs, most were male (93%) and white (71%) with an average age of 38 (IQR: 33–45) years (Fig. 3d), similar to the demographics for the overall cohort. A significantly higher proportion ($P = 0.008$) of individuals who started ART early ($n = 11$; 6% of 172 early-ART participants) achieved PTC compared to those who started ART late ($n = 2$; 1% of 195 late-ART participants). One PTC had unknown time of ART initiation relative to HIV acquisition. Among PTCs, the median CD4 + T cell count at ART interruption was 912 (IQR: 827–1219) per mm^3. If less stringent cut-off pVL thresholds were to be used of 200, 400 or 1000 copies/mL, the percentages of PTCs at day 84 would be 5%, 6% or 8%, respectively (Supplementary Fig. S4). These observations highlight that PTC is very rare, in particular among people who start ART late. In addition, while 1% of ATI participants maintained ART-free suppression for 84 days, only 0.5% regained control to pVL <50 copies/mL at 84 day when peak viremia post-ATI was higher than 10,000 copies/mL.

Factors associated with time to viremia

As seen in Fig. 4a, some of the variables associated with time to viremia were highly correlated. For instance, nadir CD4 + T cell count prior to ART start correlated with the CD4 + T cell count at ATI start (Fig. 4b; $P < 0.0001$) but also with time to viremia (Fig. 4c). There were significant positive correlations between initial viral doubling time and time to pVL >50 c/mL (Fig. 4a), and these correlations became more positive with higher viremia threshold (>400 and >10,000 c/mL, Fig. 4d–f).

In our univariable analysis, late-ART (vs early-ART) at ATI start was associated with shorter time to viremia (Supplementary Fig. S1a, b). In our multivariable analysis, late-ART remained a risk factor for shorter time to pVL >50 copies/mL (Supplementary Fig. S1a: HR 1.25, $P = 0.05$) and >10,000 copies/mL (Supplementary Fig. S1b: HR 1.61, $P < 0.01$). We observed a significantly longer time to viremia of 50 and 10,000 copies/mL for early-ART compared to late-ART initiation (Supplementary Fig. S1c, d). Similar results were found when using a threshold of time to pVL >400 copies/mL (Supplementary Fig. S5). In summary, multiple mechanistic factors may impact time to viremia after ART interruption, but in our analyses, based on clinical variables, early-ART initiation was consistently associated with both higher chance of PTC at day 84 and longer time to viremia after interrupting ART.

Powering future interventional HIV cure/remission studies

Using the calculated time to viremia and frequencies of PTC from this meta-analysis, we generated power calculations that may help inform the design of future ATI studies. We used our data as reference and calculated the number of participants needed in either a single arm or 2-group 1:1 randomized controlled trial design with a power of 90% to detect the indicated prolonged time to viremia or proportion of PTC at a 5% significant level (Fig. 5 and Supplementary Fig. S6). If the expected outcome of an intervention is a frequency of 25% PTC among early-ART participants, 36 individuals would need to be included in a single arm design and 128 individuals in a 2-group 1:1 randomized trial design (Fig. 5a). However, due to the lower observed frequency of PTC among late-ART individuals (1%), only 12 and 64 participants would be needed in a single arm design and 2-group 1:1 randomized trial design, respectively, if the expected frequency of PTC in the intervention group is 25% (Fig. 5b).

PTC is generally considered the most clinically relevant outcome in HIV cure/remission studies, but if the primary outcome is time to viremia (e.g. 50 copies/mL), 8 and 32 study participants (irrespectively of stage at ART initiation) would be needed to demonstrate a delay of at least 14 days in a single and randomized trial design, respectively (Supplementary Fig. S6a). Similarly, an expected delay in time to viremia of at least 21 days, would only require 4 and 16 individuals (irrespectively of stage at ART initiation) in a single arm and 2-group randomized trial design, respectively (Supplementary Fig. S6a). Approximately twice as many participants would be needed to demonstrate a delay of at least 14 or 21 days in time to viremia of 10,000 copies/mL (Supplementary Fig. S6b). Of note, clinical trials

https://doi.org/10.1038/s41467-025-56116-1

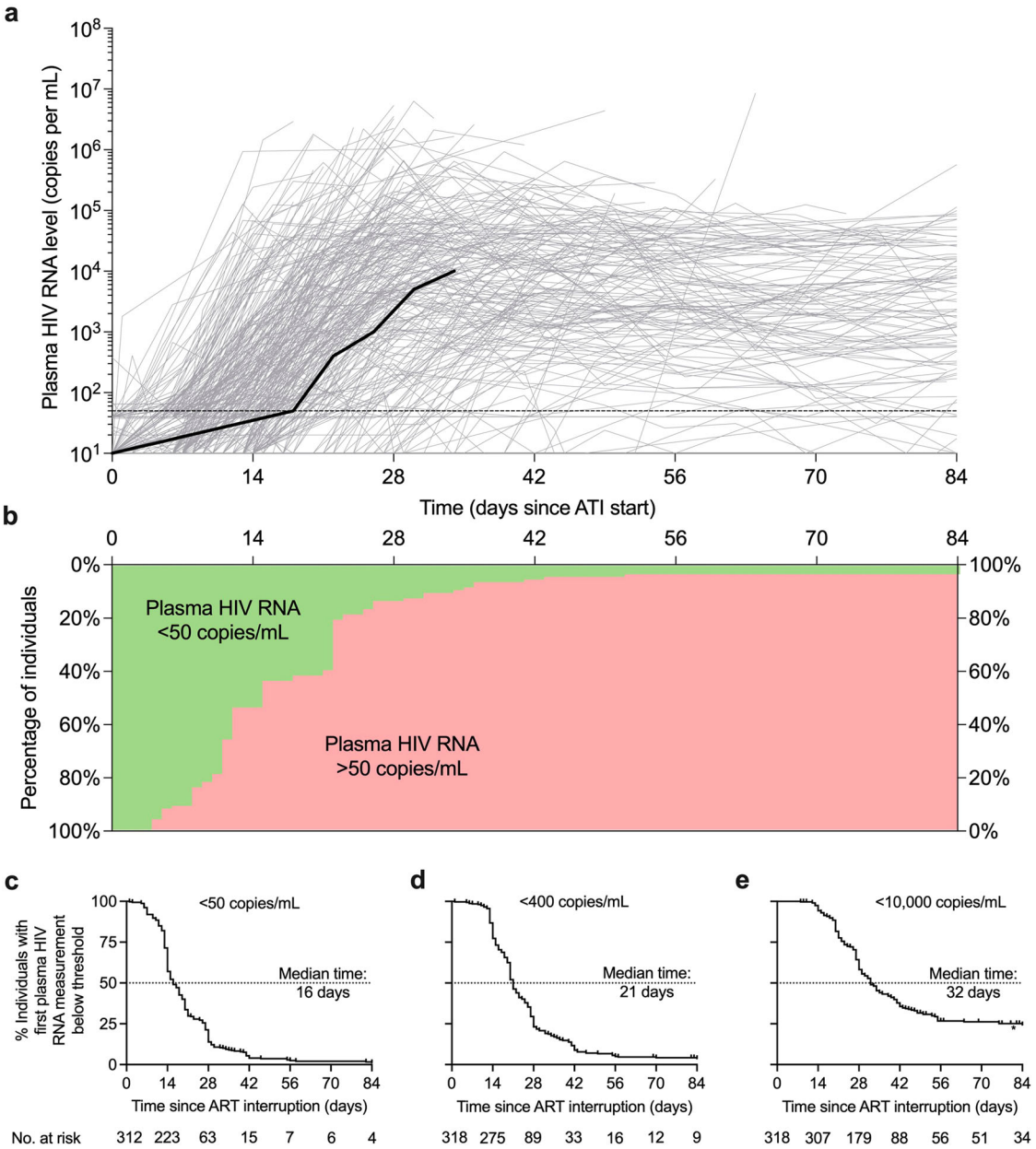


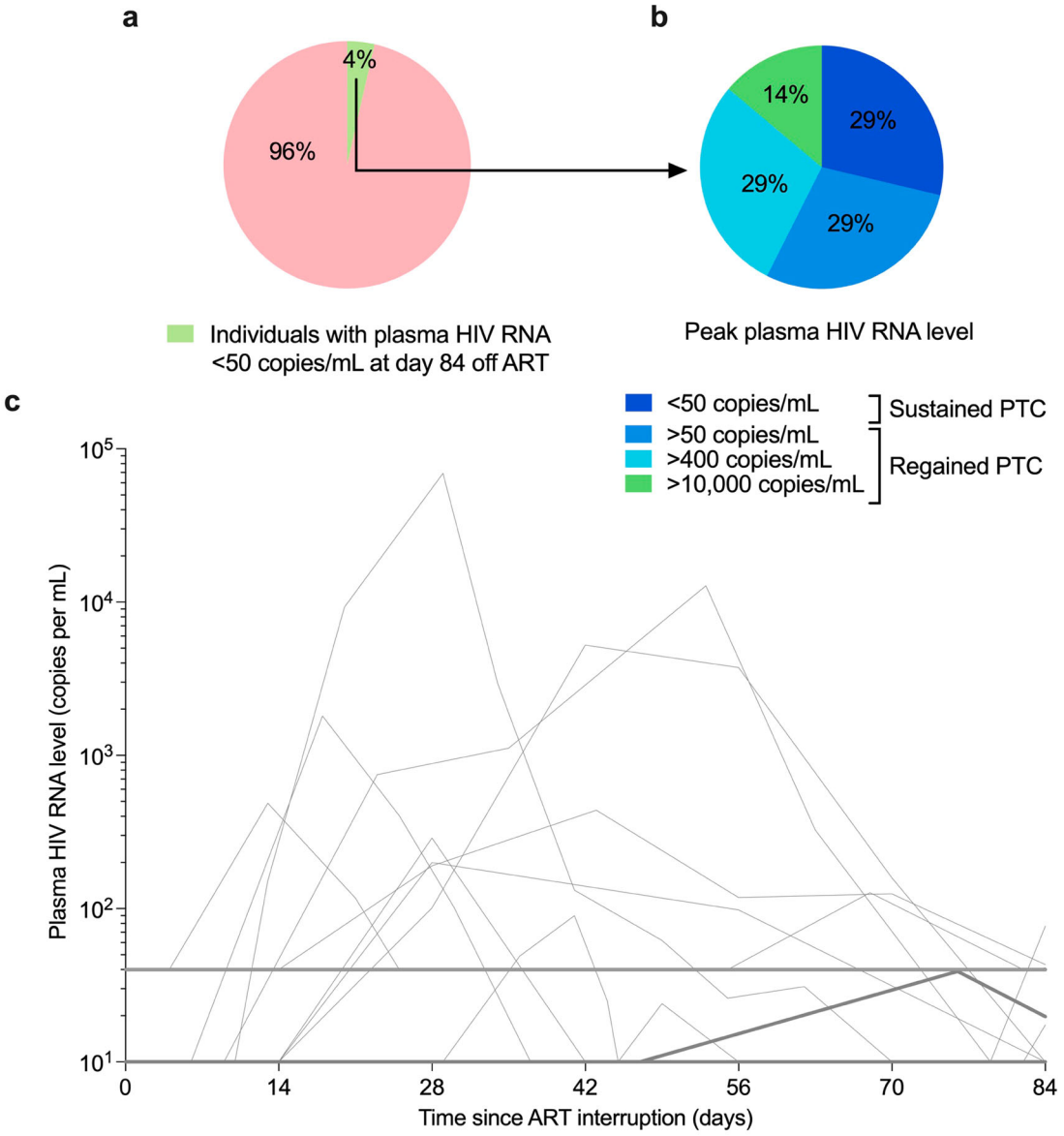
Fig. 2 | Viral kinetics, frequency of control (<50 copies/mL) and time to viremia of 50, 400 and 10,000 copies/mL during 84 days of ATI. a Individual plasma HIV RNA levels are shown during 84 days of ATI. The bold line represents median plasma HIV RNA of the entire cohort ($n = 382$). The dotted line indicates plasma HIV RNA of 50 copies/mL. Of note, 86 individuals had at least one plasma HIV RNA measurement above 100,000 copies/mL and 19 individuals had at least one plasma HIV RNA measurement above 1,000,000 copies/mL. **b** Percentage of individuals ($n = 376$) with plasma HIV RNA < 50 or >50 copies/mL during 84 days of ATI. **c**–**e** Kaplan–Meier curves showing the percentage of individuals (not NNRTI-containing regimen) with first plasma HIV RNA measurement below the following three thresholds 50, 400 and 10,000 copies/mL during 84 days of ATI. The dotted lines indicate median times to reach the specified thresholds. Below each Kaplan-Meier curves are noted the number of individuals at risk. ART antiretroviral therapy, ATI ART interruption, NNRTI non-nucleoside reverse transcriptase inhibitor.

often include slightly more participants than needed according to the power calculations to account for drop outs, typically 10–20% more. In conclusion, adequately powering of future trials is critical for optimizing resources, risk mitigation, and advancing the HIV cure/remission agenda. Our simulated power calculations show that reducing the study population size may be possible using single arm design and our extensive dataset as reference.

Discussion

This study was an individual participant data meta-analysis of 24 prospective clinical trials with 382 participants including frequent pVL measurements following an ATI. The definition of PTC in our analysis was rigorous, requiring sustained and stringent viral control off ART. We found that the median time to initial viremia above 50 copies/ml was just 16 days after ART interruption. Overall, the observed frequency of individuals with PTC defined as pVL <50 copies/ml 84 days after stopping ART was 4%. This proportion was enriched for PWH who initiated early-ART (6%), while the frequency was just 1% among those who started ART more than 6 months after HIV acquisition. Thus, our study provides robust estimates on the expected time to viremia at different thresholds as well as estimates of the frequency of PTC in a large cohort of individuals that received placebo or no active intervention prior to stopping ART. Further, we identified key clinical parameters

https://doi.org/10.1038/s41467-025-56116-1



d

PTC	Male, n (%)		Age		Race and ethnicity, n			PreART: Plasma HIV RNA [copies/mL]		PreART: Nadir CD4+ T cell count [per mm³]		PreART: Stage at ART initiation, n			At ATI start: CD4+ T cell count [per mm³]		At ATI start: ART regimen, n		
					Black	White	Other					Early	Late	Unknown			INSTI-based	PI-based	Other
Sustained (n=4)	4	(100)	42	(35;50)	0	4	0	111,067	(96,534; 125,601)	540	(509; 570)	3	1	0	1,006	(881; 1,150)	2	2	0
Regained (n=10)	9	(90)	38	(32;44)	2	6	2	38,386	(21,785; 140,000)	484	(286; 679)	8	1	1	912	(596; 1,219)	6	3	1
Total (n=14)	**13**	**(93)**	**38**	**(33;45)**	**2**	**10**	**2**	**82,000**	**(30,086; 140,067**	**484**	**(300; 600)**	**11**	**2**	**1**	**912**	**(827; 1,219)**	**8**	**5**	**1**

Data are median (interquartile ranges) unless otherwise stated.

Fig. 3 | Post-treatment control (<50 copies/mL) at day 84 of ATI. a Pie chart showing the percentage of individuals with plasma HIV RNA < 50 or >50 copies/mL at day 84 of ATI among the entire cohort ($n = 376$). **b** Pie chart showing the peak plasma HIV RNA level during 84 days of ATI among the post-treatment controllers ($n = 14$: <50 copies/mL). **c** Plasma HIV RNA levels for individuals with either sustained or regained post-treatment control (<50 copies/mL) at day 84 day of ATI. Bold and thin lines represent sustained ($n = 4$) and regained ($n = 10$) post-treatment controllers, respectively. The dotted line indicates plasma HIV RNA of 50 copies/mL. **d** Table with characteristics of the post-treatment controllers ($n = 14$: <50 copies/mL). ART antiretroviral therapy, ATI ART interruption, PI protease inhibitor, PTC post-treatment control, INSTI integrase strand transfer inhibitor.

https://doi.org/10.1038/s41467-025-56116-1

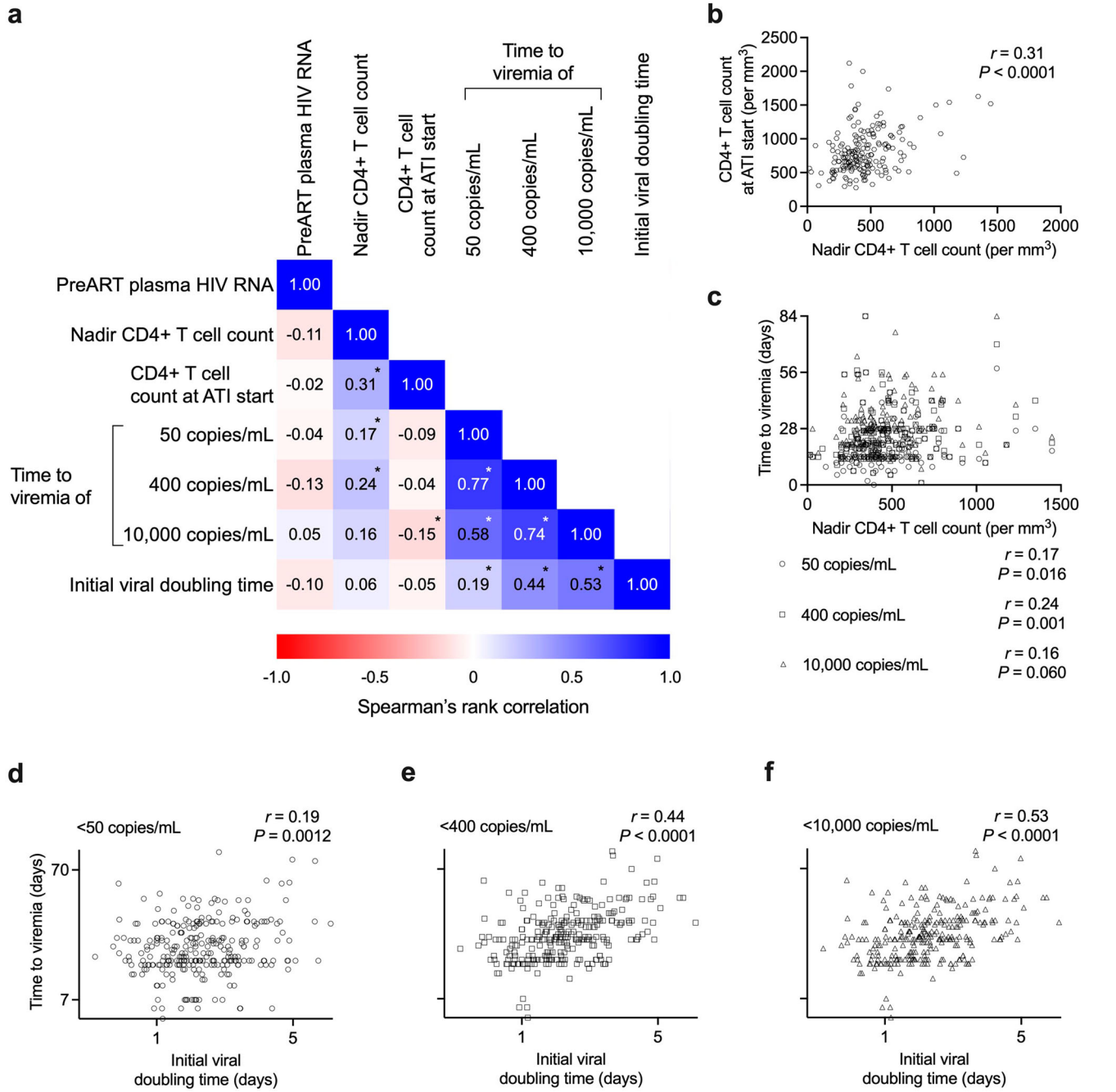


Fig. 4 | Correlations of immunological and virological variables for the ATI participants (not NNRTI-containing regimen). a Heat map of Spearman's rank correlations between immunological and virological variables for the ATI participants (not NNRTI-containing regimen). *Asterisks noted at correlations with *P* values < 0.05. **b** Correlation between nadir CD4 + T cell count and CD4 + T cell count at ATI start ($n = 206$). **c** Correlation between nadir CD4 + T cell count and time to viremia of 50 (circles; $n = 208$), 400 (squares; $n = 206$) and 10,000 (triangles; $n = 142$) copies/mL. **d**–**f** Correlations between initial viral doubling time and time to viremia of 50 (**d**, circles; $n = 357$), 400 (**e**, squares; $n = 357$) and 10,000 (**f**, triangles; $n = 261$) copies/mL, respectively. *P* values were calculated using two-tailed Spearman's correlation coefficient. ART antiretroviral therapy, ATI ART interruption, NNRTI non-nucleoside reverse transcriptase inhibitor.

associated with time to viremia and PTC that may be used in the design and interpretation of future HIV cure/remission trials.

A consistent finding in our analyses, and in agreement with others, was that starting ART less than 6 months vs more than 6 months after the time of HIV acquisition was associated with delayed time to viremia and a higher probability of PTC. Interestingly, a recent systematic review and meta-analysis estimated the overall proportion of PTC was to be as high as 8%, ranging from 3% to 15%[45]. However, these estimates were not based on individual-level data and it also included meta-data from studies that were not prospective and did not have frequent pVL monitoring which likely led to an overestimation in the frequency of PTCs. Another published meta-analysis "The CHAMP" study compared individual-level data from 6 historic ACTG ART interruption studies but not all 6 studies used as frequent pVL monitoring as in our analysis. Using a PTC definition of 2/3 of pVL measurements had to be <400 copies/mL during the first 6 months after stopping ART, the CHAMP investigators found that the timing of ART initiation also influenced the outcome with 13% vs 4% of those initiating ART in acute/recent infection vs chronic infection respectively, fulfilling their criteria for PTC at

https://doi.org/10.1038/s41467-025-56116-1

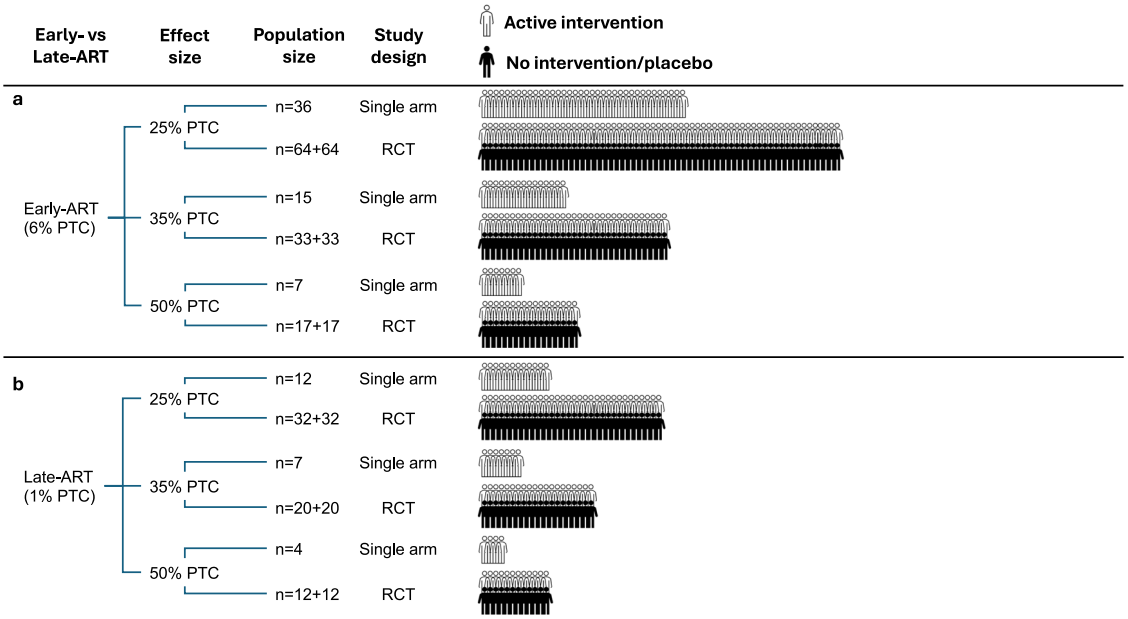


Fig. 5 | Number of participants needed in future trials to achieve 25%, 35% or 50% post-treatment control (<50 copies/mL) among early-ART and late-ART individuals at day 84 of ATI. Power calculations to be use for future study designs on how many participants would be needed for either single arm or 1:1 active intervention:placebo randomized controlled trials (RCTs) with 2 groups based on the assumption that the studies would have a power of 90% to detect the indicated differences in post-treatment control (PTC) at a 5% significant level, one-sided. Early-ART (**a**) and late-ART (**b**) defined as people who started ART within or beyond 6 months of HIV acquisition. ART antiretroviral therapy, ATI ART interruption, PTC post-treatment control.

6 months after stopping ART[10]. In another ACTG study (ACTG5345), individuals who initiated modern ART including an integrase inhibitor regimen, in either early or chronic HIV stage underwent an ATI. Whilst there was no difference in time to viral rebound between ACTG5345 ($n = 45$) and historic controls on boosted protease-inhibitor regimens, a higher percentage of early-treated participants remained off ART at week 12 post ATI compared with chronic participants (9% vs 2%; $P = 0.0496$)[30]. Thus, we conclude that in agreement with our individual data-based meta-analysis, time from HIV acquisition to ART initiation is a key determinant of subsequent ART-free virological control after ATI across different meta-analyses with varying frequency of pVL monitoring and stringency of PTC criteria.

The vast majority of individuals enrolled into the 24 prospective ATI trials included in this meta-analysis were male. This reflects the population of PWH in the global north engaged in HIV cure/remission studies but leaves behind over half the population of PWH globally. More data from diverse populations and women can be anticipated as interventional ATI studies in Africa are now ongoing[46,47]. Of note, amongst 82 African women undergoing ATI 22% maintained pVL <400 copies/mL – the pVL cut-off available at the time of study, over a median of 188 weeks after stopping ART[46]. Data from this study (SPARTAC) are not included in our analysis as pVL measurements were not recorded frequently enough to be eligible.

A limitation of this meta-analysis is that not all studies include weekly pVL measurements. Although participants included had to have at least 5 measurements of pVL within the first 84 days after ATI with a maximum of 18 days between measures within the first 42 days there are inevitably variations in timespan between measurements. Dependent on the stringency of protocol-defined ART restart criteria of each trial (e.g. pVL threshold), certain individuals may have been censored prematurely before being identified as PTC which could lead us to underestimate the frequency of PTC. However, given our finding that PTC is rare (0.5%) when the viraemic peak was >10,000 copies/mL, lower threshold pVL ART restart criteria were unlikely to have caused a large underestimation of the frequency of PTCs. The findings reflect the current research landscape, and as such are not generalizable to all PWH. This evaluation is an individual data-based meta-analysis, with the goal of being as inclusive as possible, however, only studies from the Northern Hemisphere fulfilled the inclusion criteria biasing the included population to white men. Future studies will inform the field of a wider more representative population.

Predictors of time to pVL rebound as well as magnitude of rebound have been explored. Historically, measures of the HIV reservoir have been shown to correlate with time to pVL rebound[14,15,46], and the size of the established HIV reservoir is also dependent on the time of ART initiation (early-ART vs late-ART) hence further supporting the observation that PTC is more likely in early-ART individuals[13,14,46]. In addition, several studies have found that levels of reservoir activity (i.e., cell-associated HIV RNA or residual viremia) have predicted timing of viral rebound[13,35,48]. Of the included studies in this individual data-based meta-analysis HIV reservoir measurement was assessed in 12 studies either as an inclusion criteria ($n = 4$) or secondary endpoint ($n = 8$). Since several different assays were used in these 12 studies to measure the HIV reservoir, we did not include HIV reservoir as a predictor of time to viremia. Of note, assessing the quality of the HIV reservoir seems to be more important than the quantity of the HIV reservoir[49].

Immunological biomarkers have also been demonstrated to predict time to pVL rebound. In this meta-analysis pre-ART pVL, nadir CD4 + T-cell count and CD4 + T-cell count prior to ART interruption were collected. Nadir CD4+ prior to ART start correlated with CD4 + T-cell count pre-ATI, and has previously been shown to correlate with time from HIV acquisition to ART initiation as well as size of the HIV reservoir[13] which may explain why nadir CD4 + T cell count also correlated with time to viremia. Similarly, data from the SPARTAC trial demonstrated that immunological biomarkers of T-cell exhaustion (PD-1, Tim-3 and Lag-3) measured prior to ART start predicted subsequent time to viral rebound[16]. More recently, the ACTG5345 study demonstrated that amongst 33 late-ART and 12

early-ART individuals, predictors of time and magnitude of viral rebound were high proportion of HIV-gag specific CD8 + T cells, low intact proviral HIV DNA and early-ART[13]. Detailed investigation of immunological biomarkers predictive of PTC amongst 22 individuals from 8 ACTG studies who maintained pVL <400 copies/mL for >24 weeks did not identify any association with HLA alleles, but these PTCs had compared to non-controllers lower levels of CD4+ and CD8 + T-cell activation, reduced markers of CD4 + T cell exhaustion, and more robust HIV-gag specific CD4 + T and NK cell responses[50].

In summary, to design safe and effective ATI trials, testing novel strategies and therapies towards a HIV cure/remission, inclusion of a placebo arm whilst scientifically rigorous is now debated. This meta-analysis can be informative for future study designs to inform power, strategy, monitoring frequency and communication with potential study participants to enable anticipation of potential timing and magnitude of viral rebound. The data from this meta-analysis can also help inform the aspirational "signal" threshold of a new intervention, given the rarity of spontaneous PTC. The value of smaller, focused single arm intervention trials that can compare pertinent clinical outcomes to the findings of this individual participant data meta-analysis will enable interpretation of findings. While the inclusion of control groups may be a requirement for regulatory registration of new agents, in certain settings there may no longer be ethical equipoise.

Methods

This individual data-based meta-analysis complies with all relevant ethical regulations. The 24 clinical trials included in this analysis were all conducted in accordance with the respective national competent authorities' guidelines and informed consent was obtained from all study participants (please refer to the individual studies for specific details).

Search strategy and selection criteria

We completed a literature review using the electronic database of PubMed in September 2024 using the following terms: "off therapy"[All Fields] OR "ART interruption"[All Fields] OR "treatment interruption"[All Fields] OR "Withholding Treatment"[All Fields] OR "antiretroviral interruption"[All Fields] OR "therapy interruption"[All Fields] OR "Withholding Treatment"[MeSH Terms] AND ("HIV"[Mesh]) OR ("HIV"). Several excluding terms were used to specific the search (Supplementary Table S1). No geographical restriction was applied. We excluded studies that were written in non-English, abstracts, letters, reviews, commentary articles, opinion articles, case reports, studies with co-infection, animal studies, in-vitro studies, mother-to-child transmission, infant/children and adolescent studies.

We included prospective clinical ATI studies in adults receiving either placebo or no active intervention and where frequent pVL monitoring was conducted (defined as a minimum of 5 planned pVL measurements within the first 84 days of post-ATI with a maximum of 18 days between measurements within the first 42 days).

Data extraction

Covidence.org was used for literature search. Two of the authors (JDG, JG) independently screened studies for above inclusion and exclusion criteria. To access individual-level data, corresponding authors and/or principal investigators of each identified study were asked to complete a predefined data sheet. This included individual data on age at ATI, sex (female/male/other), race and ethnicity (asian, black, white, other, unknown), pre-ART pVL, nadir CD4 + T cell count, early-ART (within 6 months) or late-ART (beyond 6 months), ART regimen at ATI, CD4 + T cell count at ATI, and consecutive pVL measurements during ATI and corresponding days since start of ATI. For six individuals the clinical assay used for quantification of pVL had a limit of quantification of 65 copies/mL, thus these individuals were excluded from the analysis of time to viremia of 50 copies/mL[24]. In a few cases, some participants from the identified studies did not fulfil the inclusion criteria and were excluded, which was noted for the respective studies.

Definitions

Early-ART versus late-ART. Early-ART initiation was defined as PWH who started ART in the presence of an HIV-positive antibody test result within up to 6 months of a previous negative antibody test, HIV + RNA or p24 in the absence of detectable antibody, or evolution of antibody testing on western blot, incident in a recency assay[51] or self-reported time of HIV acquisition less than 6 months prior to starting ART. Late-ART initiation was defined as starting ART beyond 6 months of HIV acquisition. A few individuals had unknown date of HIV acquisition and were categorized as 'unknown'.

Post-treatment control. We defined PTCs as PWH with pVL below 50, 200, 400 or 1000 copies/mL at day 84 (12 weeks) or the closest timepoint to day 84 after stopping ART. This most stringent cut-off of 50 copies/mL was chosen because it mirrors the current treatment goal for HIV and excludes viremic controllers. The pVL kinetics after stopping ART were graphed and the characteristics of PTCs including pre-ATI ART regimen were tabulated.

Statistical analysis

Data are presented as median (interquartile range [IQR]), median (range), or numbers (percentages) as indicated in each respective legend. The Kaplan–Meier estimator was used to assess the magnitude of the difference between the survival curves, and the log-rank test was used to compare time to viremia for the following three thresholds: 50, 400 and 10,000 copies/mL. Fisher's exact test was used to analyze contingency tables. For correlations, Spearman's correlation coefficient was only done for individuals with available data points. The initial viral doubling time was calculated based on the first two consecutive pVL measurements that increased, and the second measurement had to increase by 1000 copies/mL compared to the previous measurement. The slope of this increase was calculated using a linear regression model. Univariable and multivariable Cox proportional hazards regression models were used to explore the following risk factors for time to viremia during ATI: sex, early-ART versus late-ART, and ART regimen at ATI (non-nucleoside reverse transcriptase inhibitors [NNRTI] versus non-NNRTI). Correlations between initial viral doubling time and time to viremia were estimated.

Sample size estimations were calculated using either two independent study groups comparisons or one study group compared to a known value of the indicated percentages of PTC (chi-squared tests) or means of time to viremia (unpaired t tests). In the sample size estimations for randomized controlled trials, we used a randomization ratio of 1:1 active intervention:placebo in that an unbalanced randomization ratio such as 2:1 would require larger sample sizes to obtain the same precision in the statistical analysis. We estimated the size of the hypothetic study populations that would yield >90% power to detect the indicated differences at a 5% significance level using one-sided tests. We used Stata version 17.0 and Prism version 7.0 software for statistical analyses.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data are not available for download due to privacy/ethical restrictions. Specific requests for access to the data may be sent to the corresponding authors and/or principal investigators of each identified study.

References

1. Trickey, A. et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. *Lancet HIV*. **10**, e295–e307 (2023).
2. Ryom L. et al. Major revision version 11.0 of the European AIDS Clinical Society Guidelines 2021. *HIV Med*. **23**, 849–858 (2022).
3. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach [Internet]. Geneva: World Health Organization (2021).
4. Lee, M. J. et al. The RIO trial: rationale, design, and the role of community involvement in a randomised placebo-controlled trial of antiretroviral therapy plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) in participants diagnosed with recent HIV infection-study protocol for a two-stage randomised phase II trial. *Trials*. **23**, 263 (2022).
5. Ndung'u, T., McCune, J. M. & Deeks, S. G. Why and where an HIV cure is needed and how it might be achieved. *Nature*. **576**, 397–405 (2019).
6. Zheng, L., Tierney, C. & Bosch, R. J. Analytical Treatment Interruption in HIV Trials: Statistical and Study Design Considerations. *Curr HIV/AIDS Rep*. **18**, 475–482 (2021).
7. Rasmussen, T. A. et al. Panobinostat, a histone deacetylase inhibitor, for latent-virus reactivation in HIV-infected patients on suppressive antiretroviral therapy: a phase 1/2, single group, clinical trial. *Lancet HIV*. **1**, e13–e21 (2014).
8. Leth, S. et al. Combined effect of Vacc-4x, recombinant human granulocyte macrophage colony-stimulating factor vaccination, and romidepsin on the HIV-1 reservoir (REDUC): a single-arm, phase 1B/2A trial. *Lancet HIV*. **3**, e463–e472 (2016).
9. Sáez-Cirión, A. et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. *PLoS Pathog*. **9**, e1003211 (2013).
10. Namazi, G. et al. The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies. *J. Infect Dis.* **218**, 1954–1963 (2018).
11. Goujard, C. et al. HIV-1 control after transient antiretroviral treatment initiated in primary infection: role of patient characteristics and effect of therapy. *Antivir. Ther*. **17**, 1001–1009 (2012).
12. Julg, B. et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. *Lancet HIV* **6**, e259–e268 (2019).
13. Li, J. Z. et al. Predictors of HIV rebound differ by timing of antiretroviral therapy initiation. *JCI Insight* **9**, e173864 (2024).
14. Castagna, A. et al. Analytical treatment interruption in chronic HIV-1 infection: time and magnitude of viral rebound in adults with 10 years of undetectable viral load and low HIV-DNA (APACHE study). *J. Antimicrob. Chemother*. **74**, 2039–2046 (2019).
15. Williams, J. P. et al. HIV-1 DNA predicts disease progression and post-treatment virological control. *Elife*. **3**, e03821 (2014).
16. Hurst, J. et al. Immunological biomarkers predict HIV-1 viral rebound after treatment interruption. *Nat. Commun*. **6**, 8495 (2015).
17. Gunst, J. D. et al. Impact of a TLR9 agonist and broadly neutralizing antibodies on HIV-1 persistence: the randomized phase 2a TITAN trial. *Nat. Med*. **29**, 2547–2558 (2023).
18. Gruell, H. et al. Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy (ROADMAP): a randomised, open-label, phase 2A trial. *Lancet Microbe*. **3**, e203–e214 (2022).
19. Kroon, E. D. M. B. et al. A randomized trial of vorinostat with treatment interruption after initiating antiretroviral therapy during acute HIV-1 infection. *J. Virus Erad*. **6**, 100004 (2020).
20. Bilger, A. et al. Participant experiences in HIV cure-directed trial with an extended analytical treatment interruption in Philadelphia, United States. *HIV Res. Clin. Pract*. **24**, 2267825 (2023).
21. Neergaard, R. et al. "I Know That I Was a Part of Making a Difference": Participant Motivations for Joining a Cure-Directed HIV Trial with an Analytical Treatment Interruption. *AIDS Res. Hum. Retroviruses* **39**, 414–421 (2023).
22. Ugarte, A. et al. Unintended HIV-1 Infection During Analytical Therapy Interruption. *J. Infect Dis.* **221**, 1740–1742 (2020).
23. Lelièvre, J. D. & Hocqueloux, L. Unintended HIV-1 Transmission to a Sex Partner in a Study of a Therapeutic Vaccine Candidate. *J. Infect. Dis*. **220**, S5–S6 (2019).
24. Rothenberger, M. K. et al. Large number of rebounding/founder HIV variants emerge from multifocal infection in lymphatic tissues after treatment interruption. *Proc. Natl. Acad. Sci. USA*. **112**, E1126–E1134 (2015).
25. Schooley, R. T. et al. AIDS clinical trials group 5197: a placebo-controlled trial of immunization of HIV-1-infected persons with a replication-deficient adenovirus type 5 vaccine expressing the HIV-1 core protein. *J. Infect. Dis*. **202**, 705–716 (2010).
26. Rosenberg, E. S. et al. Safety and immunogenicity of therapeutic DNA vaccination in individuals treated with antiretroviral therapy during acute/early HIV-1 infection. *PLoS One*. **5**, e10555 (2010).
27. Jacobson, J. M. et al. Evidence that intermittent structured treatment interruption, but not immunization with ALVAC-HIV vCP1452, promotes host control of HIV replication: the results of AIDS Clinical Trials Group 5068. *J. Infect. Dis*. **194**, 623–632 (2006).
28. Kilby, J. M. et al. A randomized, partially blinded phase 2 trial of antiretroviral therapy, HIV-specific immunizations, and interleukin-2 cycles to promote efficient control of viral replication (ACTG A5024). *J. Infect. Dis*. **194**, 1672–1676 (2006).
29. Volberding, P. et al. Antiretroviral therapy in acute and recent HIV infection: a prospective multicenter stratified trial of intentionally interrupted treatment. *AIDS*. **23**, 1987–1995 (2009).
30. Li, J. Z. et al. Time to Viral Rebound After Interruption of Modern Antiretroviral Therapies. *Clin. Infect. Dis*. **74**, 865–870 (2022).
31. de Jong, W. et al. Therapeutic Vaccine in Chronically HIV-1-Infected Patients: A Randomized, Double-Blind, Placebo-Controlled Phase IIa Trial with HTI-TriMix. *Vaccines (Basel)*. **7**, 209 (2019).
32. Bailón, L. et al. Safety, immunogenicity and effect on viral rebound of HTI vaccines in early treated HIV-1 infection: a randomized, placebo-controlled phase 1 trial. *Nat. Med*. **28**, 2611–2621 (2022).
33. Calin, R. et al. Treatment interruption in chronically HIV-infected patients with an ultralow HIV reservoir. *AIDS*. **30**, 761–769 (2016).
34. Ruiz, L. et al. Structured treatment interruption in chronically HIV-1 infected patients after long-term viral suppression. *AIDS*. **14**, 397–403 (2000).
35. Sneller, M. C. et al. A randomized controlled safety/efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection. *Sci. Transl. Med*. **9**, eaan8848 (2017).
36. Sneller, M. C. et al. Kinetics of Plasma HIV Rebound in the Era of Modern Antiretroviral Therapy. *J. Infect. Dis*. **222**, 1655–1659 (2020).
37. Sneller, M. C. et al. Combination anti-HIV antibodies provide sustained virological suppression. *Nature*. **606**, 375–381 (2022).
38. De Scheerder, M. A. et al. HIV Rebound Is Predominantly Fueled by Genetically Identical Viral Expansions from Diverse Reservoirs. *Cell Host Microbe*. **26**, 347–358.e7 (2019).

39. Gunst, J. D. et al. Early intervention with 3BNC117 and romidepsin at antiretroviral treatment initiation in people with HIV-1: a phase 1b/2a, randomized trial. *Nat. Med.* **28**, 2424–2435 (2022).
40. Leal, L. et al. Effect of Intranodally Administered Dendritic Cell-Based HIV Vaccine in Combination With Pegylated Interferon α-2a on Viral Control Following ART Discontinuation: A Phase 2A Randomized Clinical Trial. *Front. Immunol.* **12**, 767370 (2021).
41. Papasavvas, E. et al. Randomized, controlled trial of therapy interruption in chronic HIV-1 infection. *PLoS Med.* **1**, e64 (2004).
42. Pannus, P. et al. Rapid viral rebound after analytical treatment interruption in patients with very small HIV reservoir and minimal on-going viral transcription. *J. Int. AIDS Soc.* **23**, e25453 (2020).
43. Tipoe, T. et al. Impact of antiretroviral therapy during primary HIV infection on T-cell immunity after treatment interruption. *Eur. J. Immunol.* **54**, e2451200 (2024).
44. Jacobson, J. M. et al. Dendritic Cell Immunotherapy for HIV-1 Infection Using Autologous HIV-1 RNA: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *J. Acquir. Immune Defic. Syndr.* **72**, 31–38 (2016).
45. Zhou, C. et al. Factors associated with post-treatment control of viral load in HIV-infected patients: a systematic review and meta-analysis. *Int. J. Infect. Dis.* **129**, 216–227 (2023).
46. Gossez, M. et al. Virological remission after antiretroviral therapy interruption in female African HIV seroconverters. *AIDS*. **33**, 185–197 (2019).
47. Le, C. N. et al. Time to viral rebound and safety after antiretroviral treatment interruption in postpartum women compared with men. *AIDS*. **33**, 2149–2156 (2019).
48. Li, J. Z. et al. The size of the expressed HIV reservoir predicts timing of viral rebound after treatment interruption. *AIDS*. **30**, 343–353 (2016).
49. Gasca-Capote, C. et al. The HIV-1 reservoir landscape in persistent elite controllers and transient elite controllers. *J. Clin. Invest.* **134**, e174215 (2024).
50. Etemad, B. et al. HIV post-treatment controllers have distinct immunological and virological features. *Proc. Natl. Acad. Sci. USA*. **120**, e2218960120 (2023).
51. Yufenyuy, E. L. et al. Performance evaluation of the Asante Rapid Recency Assay for verification of HIV diagnosis and detection of recent HIV-1 infections: Implications for epidemic control. *PLOS Glob. Public Health.* **2**, e0000316 (2022).

Acknowledgements

We thank all study participants who devoted time to research. The authors would also like to thank to Meghan K. Rothenberger, Michael C. Sneller, Sabine Allard and Eric Florence for providing data. The authors who undertook this research were funded by awards from the following funders; the Lundbeck Foundation (J.D.G.: R381–2021–1405 and O.S.S.: R313-2019-790), Danish Council for Independent Research (O.S.S.: #9060-00023B), Central Region Denmark Research Fund (O.S.S.), Work supported by AELIX Therapeutics and partly by grants from the Spanish Research Agency and the European Reginal Development Fund (B.M.: RTC-2017-6473-1), National Institute of Health (NIH) (L.J.M.: UM1 AI164570), National Institute of Allergy and Infectious Diseases (L.J.M.: NIH AI48398), the Philadelphia Foundation (L.J.M.: Robert I. Jacobs Fund), The Stengel-Miller family (L.J.M.), AIDS funds from the Commonwealth Universal Research Enhancement Program Pennsylvania, Department of Health (L.J.M.), the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases, NIH (T.W.C.), NIH (C.B.: P01 AI178375 *OMIT-HIV)*, European Union´s Horizon Europe Research and Innovation Programme (C.B.: GA 101057548 (*EPIVINF*) and B.M.: 681137-EAVI2020, NIH grant P01-AI131568 and by ISCIII PI20/01039), NIH/NIAID (J.M.P.: 1 UM1 AI164561-01, USA), EU grant (R.A.G.: FP7-HEALTH-2013-INNOVATION-1 Proposal No: 602570-2), Fondo Europeo para el Desarrollo Regional (FEDER) (R.A.G.), the SPANISH AIDS Research Network (R.A.G.: RD16/0025/0002– ISCIII – FEDER (RIS)), the CERCA Programme / Generalitat de Catalunya SGR 615 and SGR 653 (R.A.G.), NIAID (J.L.I., R.B. and ACTG A5345: AI068634, UM1 AI068636, UM1 AI106701),NIH (J.L.I.: AI150396, AI169768, AI060354), Spanish Ministry of Economy (MINECO) (L.L.: SAF2015-66193-R, SAF-2017-88089-R, and RTI2018-096309-B-I00), FP7-HEALTH-2013-INNOVATION-1 Proposal No: 602570-2 (L.L.), the Foundation for AIDS Research (J.F.: amfAR, grant ID 109842-65-RGRL), Bill and Melinda Gates Foundation (J.G. and S.F.: grant OPP1204692), Imperial College London (J.G. and S.F.), NIHR Biomedical Research centre at Imperial College Healthcare National Health Service Trust (J.G. and S.F.). None of the specific sources of funding had any role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Author contributions

J.D.G., O.S.S. and S.F. developed the study design. J.L.I., R.J.B., A.W., C.S., T.W.C., B.M., K.G., L.P., M.A.D.S., L.V., K.E., A.T., T.S., D.S.G., C.B., E.P., L.J.M., J.M.P., R.C., A.C., C.M., W.d.J., L.L., F.G., R.A.G., T.T., J.F. provided data and input to the statistical analysis. J.D.G. did the statistical analysis. J.D.G. and J.G. drafted the tables and figures. J.D.G., J.G., O.S.S. and S.F. drafted the article, which all authors critically revised for important intellectual content.

Competing interests

The authors declare no conflict of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-025-56116-1.

Correspondence and requests for materials should be addressed to Jesper D. Gunst.

Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.

Jesper D. Gunst[1,2,29] ✉, Jesal Gohil[3,29], Johanthan Z. Li[4], Ronald J. Bosch[5], Andrea White, Catherine Seamon[6], Tae-Wook Chun[7], Beatriz Mothe[8,9,10,11], Kathleen Gittens[12], Lauren Praiss[7], Marie-Angélique De Scheerder[13], Linos Vandekerckhove[14], Kevin Escandón[15,16], Ann Thorkelson[16], Timothy Schacker[15,16], Devi SenGupta[17], Christian Brander[8,10,11,18,19], Emmanouil Papasavvas[20], Luis J. Montaner[20], Javier Martinez-Picado[8,10,11,19], Ruxandra Calin[21], Antonella Castagna[22,23], Camilla Muccini[22], Wesley de Jong[24], Lorna Leal[25,26,27], Felipe Garcia[25,26,27], Rob A. Gruters[24], Timothy Tipoe[28], John Frater[28], Ole S. Søgaard[1,2,29] & Sarah Fidler[3,29]

[1]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark. [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. [3]Department of Infectious Disease Imperial College London, Imperial College NIHR BRC, London, UK. [4]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [5]Harvard T.H. Chan School of Public Health, Boston, MA, USA. [6]Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, MD, USA. [7]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. [8]IrsiCaixa Immunopathology Research Institute, Badalona, Spain. [9]Department of Infectious Diseases and Fundació Lluita contra les Infeccions, Hospital Universitari Germans Trias I Pujol, Badalona, Barcelona, Spain. [10]CIBER de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain. [11]Department of Infectious Diseases and Immunity, University of Vic – Central University of Catalonia (UVic-UCC), Barcelona, Spain. [12]Clinical Center, National Institutes of Health, Bethesda, MD, USA. [13]Department of General Internal Medicine, Ghent University Hospital, Ghent, Belgium. [14]HIV Cure Research Center, Department of General Internal Medicine, Ghent University Hospital, Ghent University, Ghent, Belgium. [15]Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, USA. [16]Department of Medicine, University of Minnesota, Minneapolis, USA. [17]Gilead Sciences, Inc, Foster, USA. [18]AELIX Therapeutics, Barcelona, Spain. [19]Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain. [20]The Wistar Institute, Philadelphia, PA, USA. [21]Department of Infectious Diseases, Tenon Hospital, Sorbonne University, AP-HP, Paris, France. [22]Infectious Diseases, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) San Raffaele Scientific Institute, Milan, Italy. [23]Vita-Salute San Raffaele University, Milan, Italy. [24]Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands. [25]Infectious Diseases Department, Hospital Clínic Barcelona, Barcelona, Spain. [26]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain. [27]Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain. [28]Nuffield Dept of Medicine, University of Oxford, UK and NIHR Oxford Biomedical Research Centre, Oxford, UK. [29]These authors contributed equally: Jesper D. Gunst, Jesal Gohil, Ole S. Søgaard, Sarah Fidler. ✉e-mail: jesper@gunst.dk