Intensifying Antiretroviral Therapy With Raltegravir and Maraviroc During Early Human Immunodeficiency Virus (HIV) Infection Does Not Accelerate HIV Reservoir Reduction

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Background. Persistent human immunodeficiency virus (HIV) within the CD4^{+} T-cell reservoir is an obstacle to eradication. We hypothesized that adding raltegravir and maraviroc to standard combination antiretroviral therapy (cART) during early HIV infection could substantially reduce viral reservoirs as a step towards eradication.

Methods. A prospective, randomized, double-blinded, placebo-controlled pilot trial enrolled 32 participants with documented early (<6 months) HIV infection to either standard cART (emtricitabine/tenofovir/lopinavir/ritonavir) or intensive cART (standard regimen + raltegravir/maraviroc). Human immunodeficiency virus reservoirs were assessed at baseline and at 48 weeks by (1) proviral DNA, (2) cell-associated RNA, and (3) replication-competent virus, all from purified blood CD4^{+} T cells, and (4) gut proviral DNA. A multiassay algorithm (MAA) on baseline sera estimated timing of infection.

Results. Thirty individuals completed the study to the 48-week endpoint. The reduction in blood proviral burden was −1.03 log DNA copies/10[6] CD4^{+} T cells versus −.84 log in the standard and intensive groups, respectively ($P = .056$). Overall, there was no significant difference in the rate of decline of HIV-associated RNA, replication-competent virus in blood CD4^{+} T cells, nor proviral gut HIV DNA to 48 weeks. Individuals who presented with more recent HIV infection had significantly lower virus reservoirs, and cART tended to reduce their reservoirs to a greater extent.

Conclusions. Intensive cART led to no additional reduction in the blood virus reservoir at 48 weeks compared with standard cART. Human immunodeficiency virus reservoir size is smaller earlier in HIV infection. Other novel treatment strategies in combination with early cART will be needed to eliminate the HIV latent reservoir.

Keywords. acute; early; HIV; intensive cART; reservoir.

The potential benefits of antiretroviral treatment during primary human immunodeficiency virus (HIV) infection are still under investigation [1]. Although treatment

of acute infection may have a beneficial effect on disease progression [2–4], a major hurdle to HIV eradication is virus persistence in a latent, replication-competent form in various reservoirs that are established soon after acute infection [1, 5–7], particularly within resting CD4^{+} T cells [8]. Individuals who initiate standard 3-drug combination antiretroviral therapy (cART) at the time of early HIV infection (infected <6 months) have a lower peripheral blood HIV reservoir burden as measured by proviral DNA [8–12] or replication-competent HIV [11, 12] than those who start cART during chronic HIV infection (infected > 1 year).

The ultimate goal of treatment of early HIV would be to prevent establishment of tissue reservoirs and to

eradicate the virus, and more intensive and potent regimens of antiviral therapy may help to achieve this. The development of newer classes of drugs targeted at steps prior to viral entry (such as maraviroc) and viral integration (such as raltegravir) raises the possibility that cART intensification with these agents may lead to a more rapid and complete suppression of viral reservoirs. We hypothesized that the addition to cART of an integrase inhibitor (raltegravir) and an entry inhibitor, maraviroc, during early HIV infection might substantially reduce viral reservoirs compared with a standard cART regimen, enhancing virologic control and opportunities for eradication.

MATERIALS AND METHODS

Study Participants
Participants were enrolled at Maple Leaf Medical Clinic (Toronto, Canada). Individuals with acute/early HIV infection were defined by one of the following criteria: (1) positive HIV antibody test result (Western blot), and documented negative test in previous 6 months; or (2) positive/weakly positive HIV enzyme-linked immunosorbent assay (ELISA), with indeterminate or evolving Western blot with demonstrated HIV antigenemia (p24) or viremia (HIV viral load ≥ 500 copies/mL); or (3) negative HIV antibodies in the setting of an illness compatible with acute seroconversion with demonstrated p24 antigenemia or plasma viremia; or (4) a compatible clinical history of a recent seroconversion illness within the last 6 months, with a documented high-risk exposure within 6 months, with a negative HIV antibody test within the last year. Written informed consent was obtained. The study was approved by the University of Toronto and St. Michael's Hospital research ethics boards. The study was registered with ClinicalTrials.gov number NCT01154763.

Study Design and Treatment Regimen
The trial is a prospective, randomized, double-blinded, placebo-controlled pilot study. A total of 32 individuals were randomized 1:1 to one of two arms: the "intensive" arm with standard cART (emtricitabine 200 mg/tenofovir 300 mg QD + lopinavir 400 mg/ritonavir 100 mg BID) + raltegravir 400 mg BID and maraviroc 150 mg BID or the "placebo" or "standard" arm with standard cART. Before initiation of treatment, viral genotype and genotypic tropism profile were determined to ensure effectiveness of therapy. For intolerance or resistance to lopinavir/ritonavir, efavirenz or darunavir/ritonavir was used. Individuals were excluded if virus used CXCR4 by genotype. Leukopheresis to obtain peripheral blood mononuclear cells (PBMC) for reservoir testing and optional sigmoid gut biopsies were obtained at baseline and at 48 weeks of treatment. The sigmoid colonic biopsies were sampled approximately 30 cm from the anal verge. Approximately 20 sigmoid biopsies were collected at each visit. Gut mononuclear cells were enriched for CD4+

T cells using CD8 depletion with magnetic beads (Dynal, Life Technologies, Carlsbad, CA). Approximately 4–8 million gut mononuclear cells were recovered after CD8 depletion and subsequently frozen down in 0.5 to 1.0 million cell aliquots.

Randomization
Study numbers were randomly generated by a statistician not associated with the study using variable block sizes. When a patient was determined to be eligible by the study coordinator and consented, the subject was allocated the next study number in which study medications were already pre-prepared by pharmacy.

Endpoints
The primary endpoint for the analysis was the change in proviral HIV DNA in total CD4+ T cells in blood from baseline to week 48. After the endpoint was reached and primary endpoint data were analyzed, participants were notified of the endpoint results, and at that time they were given the option to maintain or simplify their regimens. All participants elected to simplify their regimens.

Serology Studies
To further define the timing of HIV infection, baseline sera were tested using a multiassay algorithm (MAA) as previously described [13]. Sera were tested with the BED-Capture EIA assay (Calypte Biomedical, Lake Oswego, OR), and average normalized optical density (OD-n) was calculated. Antibody avidity of sera was measured using a modified Genetic Systems ½+O ELISA (Bio-Rad, Hercules, CA). Individuals were classified as having recent infection (MAA+) based on a BED-CEIA of <1.0 OD-n, and an avidity index of <80%, a positive viral load, and a CD4 count >200 cells/μL. Participants with baseline samples that did not meet these criteria were classified as MAA−. Previous studies demonstrated that the mean duration of recent infection based on those criteria was 141 days from seroconversion [13].

Virological Studies
Quantitation of Human Immunodeficiency Virus Proviral DNA
The frequency of CD4+ T cells carrying HIV proviral DNA was determined by real-time polymerase chain reaction (PCR) as previously described [14] using genomic DNA from 2×10^6 purified CD4+ T cells (QIAGEN, Valencia, CA). One microgram of DNA was used as the template for real-time PCR in a 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA). Polymerase chain reaction was performed in triplicate using HIV-specific primers and probe, RNaseP-specific primers and probe (VIC) (Applied Biosystems), and TaqMan gene Expression Master Mix (Applied Biosystems) in 50 μL. The following primers were used for amplification of HIV long terminal repeat: 5′-GGTCTCTCTGGTTAGACCAGAT-3′ (5′ primer)

and 5′-CTGCTAGAGATTTTCCACACTG-3′ (3′ primer) along with the fluorescent probe 5′-6FAM-AGTAGTGTGTG CCCGTCTGTT-TAMRA-3′. Polymerase chain reaction conditions were 95°C for 10 minutes; 45 cycles of 15 seconds at 95°C; 1 minute at 60°C. Serially diluted ACH-2 DNA was used to obtain standard curves. The detection limit of the assay was 2.6 copies of HIV DNA.

Cell-Associated Human Immunodeficiency Virus RNA

To detect unspliced HIV RNA, total cellular RNA was isolated from $2-5 \times 10^6$ CD4$^+$ T cells by using RNeasy Mini Kit (QIAGEN). Synthesis of complementary DNA (cDNA) and real-time PCR were performed in 7500 Real-Time PCR System (Applied Biosystems) by using TaqMan RNA-to-Ct 1-Step Kit (Applied Biosystems). Polymerase chain reaction conditions were as follows: cDNA synthesis at 45°C for 10 minutes, denaturation at 95°C for 10 minutes; 45 cycles of 15 seconds at 95°C; 1 minute at 60°C. The following primers and probe were used: 5′-TCTCTAGCAGTGGCGCCCGAACA-3′ (5′ primer), 5′-TCT CCTTCTAGCCTCCGCTAGTC-3′ (3′ primer), and 5′-6FAM-CAAGCCGAGTCCTGCGTCGAGAG-TAMRA-3′ (probe). Serially diluted in vitro-transcribed HIV RNA was used to obtain standard curves. The limit of detection of the assay is 10 RNA template copies/assay.

Quantitative Coculture Assays

To determine the frequency of CD4$^+$ T cells carrying replication-competent HIV, quantitative coculture assays were done as described previously [15]. Highly enriched CD4$^+$ T cells (>97% purity) were enumerated using Guava PCA (Guava Technologies) and were seeded to tissue culture plates. Irradiated PBMCs (8×10^6) from HIV-negative donors were added to each well along with anti-CD3 antibody and incubated overnight in medium including recombinant interleukin-2 (20 units/mL). CD8-depleted and anti-CD3 stimulated PBMC blasts (1×10^6) from HIV-negative donors were added to each well the following day and on day 7. The culture supernatants were subjected to HIV p24 ELISA between days 14 and 21. The infectious units per million cells (IUPM) values were determined as previously described [16].

Statistics
Sample Size Considerations

For this pilot study, 32 individuals were chosen to be randomized to both arms (14 plus 2 for attrition/arm). A sample size of 14 per group would achieve 82% power to detect 0.5 log HIV-DNA copies/million cells difference with the null hypothesis that the mean log differences in the 2 treatment groups are the same and the alternative hypothesis that the intensive group achieves additional 0.5 log drop in HIV-DNA copies/million cells 48 weeks after initiation of cART, with estimated standard deviations of 0.5 in each group and with a significance level

(alpha) of 0.10 using a 2-sided 2-sample t test. Baseline group comparisons were made with Student's t test or Wilcoxon rank-sum or Fisher's exact test, as appropriate. Differences in viral reservoir reduction between groups at week 48 were assessed using linear regression adjusted for baseline viral reservoir.

RESULTS

Study Participants

Forty-six participants with a diagnosis of recent HIV infection (see definition above) were screened for eligibility in the study (Figure 1). Of these, 32 met all inclusion criteria and were provided with either the standard or intensive cART regimen. Of those randomized, 2 participants in the intensive regimen did not complete the study due to moving out of province or loss of follow-up. Thus, 30 individuals completed the study to the 48-week endpoint (baseline demographic characteristics; Table 1). Twenty-seven participants were HIV Western blot positive and 3 were HIV Western blot indeterminate at presentation. Approximately 70% of participants in both groups were classified as recent infection (MAA$^+$) at baseline (see Methods). From previous work, MAA positivity correlates with recent infection with a median time 141 days from seroconversion [13]. Thus, individuals who were positive by the MAA were more likely to have been infected for less time than those MAA$^-$ individuals in this population of individuals known to be infected <6 months. No difference in adverse events were observed between groups. Two participants in the placebo group and 1 participant in the intensive group switched their backbone protease inhibitor from kaletra/ritonavir to darunavir/ritonavir, as per protocol, due to diarrhea. One participant in the intensive group developed severe transient neutropenia at 60 weeks (after primary endpoint), which was not believed to be related to study medication.

Human Immunodeficiency Virus Plasma Viral Loads and CD4 Count Responses to Treatment

There was a nonsignificant trend to more rapid decline in plasma viral load in the intensive treatment group (Figure 2). The median time to first undetectable viral load was 4 weeks in the intensive arm vs 12 weeks in the standard treatment arm ($P = .094$, Wilcoxon rank-sum test). There were no differences in CD4 or CD8 counts between groups at baseline ($P = .53$ and 0.25, respectively); at 48 weeks, the median CD4 counts were 765 vs 730/mm^3 ($P = .917$, Wilcoxon rank-sum test) and median CD8 counts were 825 vs 915/mm^3 ($P = .819$, Wilcoxon rank-sum test) for intensive vs standard arms, respectively.

Human Immunodeficiency Virus Reservoir Analysis
Proviral Burden in Peripheral Blood CD4$^+$ T Cells

At baseline, the proviral burden in peripheral blood CD4$^+$ T cells from the intensive group was a median of 1642 (log 3.21;
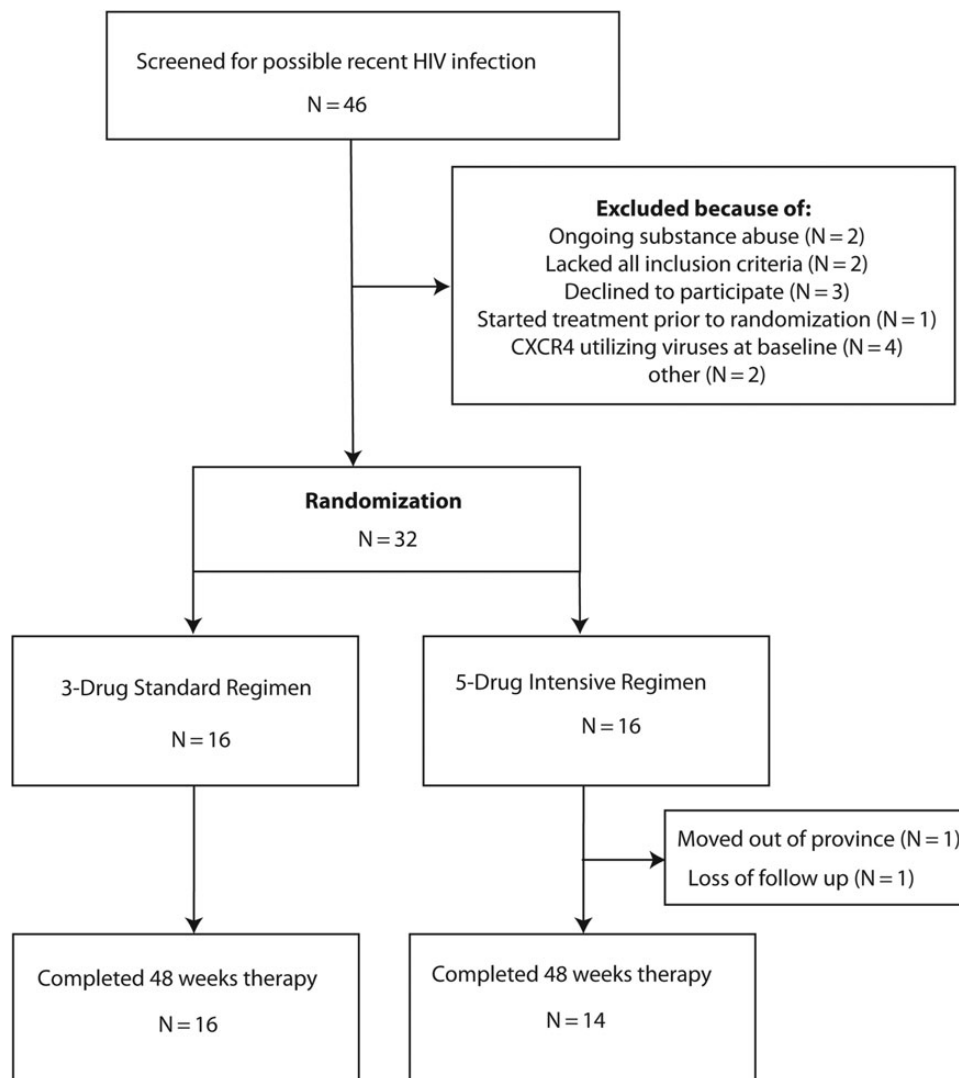
Figure 1. Subject recruitment and follow-up. Abbreviation: HIV, human immunodeficiency virus.

mean = 3734) with a range of 183 to 14 918 HIV DNA copies/10^6 CD4$^+$ T cells; this was not significantly different from the placebo arm, with a median of 2131 (log 3.33; mean = 4625) and a range of 86 to 21 298 HIV DNA copies/10^6 CD4$^+$ T cells (Figure 3A; P = .591). At 48 weeks, the median provirus levels in the intensive group were 279 HIV DNA copies/10^6 CD4$^+$ T cells (log 2.44; mean = 558; range, 26–2836) vs 244 HIV DNA copies/10^6 CD4$^+$ T cells (log 2.39; mean = 631; range, 2.5–5186) in the standard group (Figure 3A). Therefore, the median proviral burden had dropped by 1.03 log DNA copies/10^6 CD4$^+$ T cells in the standard group and by 0.84 logs in the intensive group. The estimated difference in mean change from baseline to 48 weeks between groups was 0.20 log DNA copies/10^6 CD4$^+$ T cells in favor of the standard treatment group (95% confidence interval [CI]: −0.006 to 0.40; P = .056, linear regression). It is interesting to note that the P value

approaching significance is driven by 1 subject in the standard treatment group who became undetectable at 48 weeks. If this subject is removed, the differences between groups reduced to 0.14 and give a P = .152.

Human Immunodeficiency Virus-Associated RNA in Peripheral Blood CD4$^+$ T Cells

Cell-associated HIV RNA was examined in peripheral blood isolated CD4$^+$ T cells at baseline, 24 and 48 weeks (Figure 3B). Human immunodeficiency virus RNA within blood CD4$^+$ T cells dropped from a median of 750 (mean = 1675) copies/µg CD4$^+$ T cell RNA at baseline to a median of 20 (mean = 65) copies/µg RNA at 48 weeks in the intensive group, compared to a median 1064 (mean = 2849) copies/µg RNA at baseline to 29 (mean = 99) copies/µg RNA at 48 weeks in the placebo group. These reductions were not statistically significant between groups (estimated

Table 1. Baseline Characteristics

	Standard cART (n = 16)	Intense cART (n = 14)	P Value
% male	100	100	n/a
% MSM	100	100	n/a
Mean age (years, range)	30 (22–59)	34 (23–49)	.787[a]
Duration of Infection by MAA			
MAA+	10 of 16 (62.5%)	10 of 14 (71%)	.71[b]
MAA−	6 of 16 (37.5%)	4 of 14 (29%)	.71[b]
CD4 count (cells/µL, range)	581 (490–1370)	581 (250–960)	.533[a]
Mean log baseline Viral load ($\log_{10}$ copies/mL, range)	4.31 (3.24–5.4)	4.30 (3.21–5.35)	.981[a]

Abbreviations: cART, combination antiretroviral therapy; MAA, multiassay algorithm for recent infection; MSM, men who have sex with men; n/a, not applicable.

[a] P value based on Wilcoxon rank-sum test.

[b] P value based on Fisher's exact for MAA.

difference in mean change between groups, was −0.12 $\log_{10}$ copies of HIV/µg RNA, ie, in favor of intensive group, 95% CI: −0.43 to 0.19; P = .451, using linear regression).

Levels of Replication Competent Virus in CD4+ T-Cell Reservoirs

We performed quantitative HIV coculture in resting CD4+ T cells at baseline and at week 48 (n = 13 evaluated in intensive group due to inadequate sample from 1 participant, n = 16 evaluated in standard group) (Figure 3C). At baseline, the intensive group had a median of 41 (mean = 103.02; range, 0.51–420.55) IUPM CD4+ T cells and the standard group had a median of 16.25 (mean = 97.41; range, 1.61–747.04) IUPM CD4+ T cells, which were not statistically significant at baseline (P = .659). At week 48, the intensive group had a median of 0.5 (mean = 2.19; range, 0.05–16.25) IUPM and the standard group had a median of 0.51 (mean = 1.41; range, 0.04–8.08) IUPM. Although the intensive treatment group tended to have a steeper rate of decline in IUPM at week 48, this was not statistically significant (estimated difference in median change between groups, −0.17 in favor of intensive, 95% CI: −0.66 to 0.32; P = .486, linear regression) (see Figure 3C). There were 2 individuals who showed no decline in IUPM at week 48 (subjects no. 5318, intensive arm and no. 5290, standard arm). Neither had baseline genotypic resistance. Subject 5290 became plasma RNA undetectable by week 24 and was noted to have issues with adherence (missed some doses). Subject 5318 was plasma RNA undetectable at week 4. Subject 5318, although compliant with medication, had gastrointestinal intolerance to lopinavir, which was switched to a darunavir-based regimen at week 8.

Gut Proviral DNA Burden

Nineteen individuals had evaluable sigmoid gut biopsies at baseline and week 48 (11 intensive, 8 standard) (see Figure 3D). At baseline, the intensive group had a median of 761.80 (mean = 2617.36; range 119.92–15921.25) proviral copies/million CD8+-depleted cells and the standard group had a median of 1529.98 (mean = 2187.50; range, 146.49–6767.30) proviral copies/million CD8+-depleted cells (P = .804). At week 48, the intensive group had a median of 139.91 (mean = 286.59; range, 53.23–1044.36) vs the standard group median of 137.79 (mean = 351.30; range, 52.22–1344.89) proviral copies/million CD8+-depleted cells (Figure 3D). The change in median proviral gut loads from baseline to 48 weeks was −0.82 $\log_{10}$ units (range, −0.97 to −0.55) for the intensive group vs −0.76 $\log_{10}$ units (range, −0.99 to −0.54) for the standard group (P = .632).

Effect of Treatments on Duration of Human Immunodeficiency Virus Infection at Presentation

Although all enrolled subjects had early HIV infection defined as being infected within 6 months at presentation, we further characterized recent infection using an MAA that uses HIV antibody avidity. Previous studies demonstrated that the mean duration of recent infection on sera that were MAA+ was 141 days from seroconversion [13].

Based on the MAA, we stratified individuals who were likely infected (1) more recently (intensive = 10, placebo = 10) and (2) less recently (intensive = 4, placebo = 6). As expected, those presenting later in infection (MAA−) had higher baseline levels of HIV proviral DNA, cell-associated HIV RNA, and replication-competent virus from resting CD4+ T cells (Figure 4). In addition, viral reservoirs at baseline correlated with HIV antibody avidity, where lower avidity antibodies observed earlier in infection were associated with lower reservoirs (data not shown). Gut proviral DNA levels showed considerable variability between individuals, and these were not statistically different comparing timing of presentation (data not shown). For proviral burden, surprisingly, we saw a greater treatment effect of the standard therapy compared with intensive therapy in the MAA+ group from baseline to week 48 (mean reduction 0.81 log vs 1.09 log, intensive vs standard, respectively; P = .031) (Figure 5). The estimated difference in mean change between groups is 0.27 (P = .031, linear regression). In the standard and MAA+ group, 1 subject (no. 5285) was noted whose DNA dropped to undetectable at week 48 (see Figure 5). Without this subject, the estimated difference in mean change between intensive versus standard within MAA+ is much smaller (0.18 log), and the P changed to .107. Thus, these differences are mainly driven by 1 subject. There was no significant difference between treatment effect in the MAA− group (mean reduction 0.80 log vs 0.88 log, intensive vs standard, respectively;
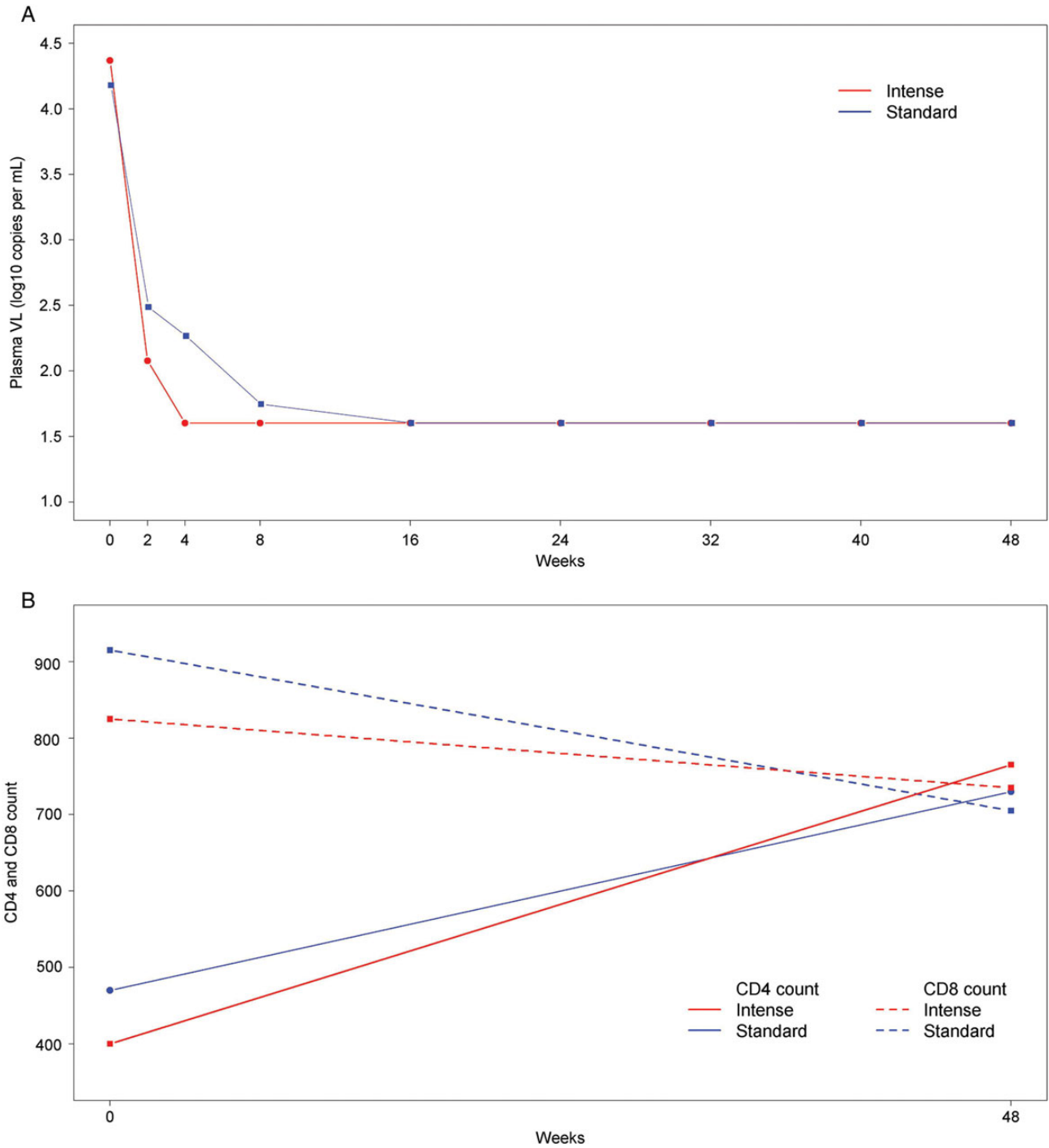
Figure 2. Effect of treatments on plasma viral load and peripheral CD4/CD8 counts. Plasma virus load kinetics on treatment for 30 subjects completing primary endpoint shown in (A) and CD4 and CD8 counts at baseline and 48 weeks in (B). Medians are depicted.

$P = .688$). For CD4$^+$ T cell-associated HIV RNA, or HIV viral culture from resting cells, there was no significant difference between treatments for either the MAA$^+$ or MAA$^-$ groups (data not shown). We asked whether there was a more potent treatment effect of either regimen on viral reservoirs if given to individuals presenting MAA$^+$ compared with MAA$^-$.

After adjusting for baseline reservoirs, we observed that the drop in reservoirs (HIV DNA, HIV RNA, or replication-competent virus from blood) at week 48 in the MAA$^+$ group tended to be greater than in the MAA$^-$ group, but these differences were not statistically significant (data not shown).
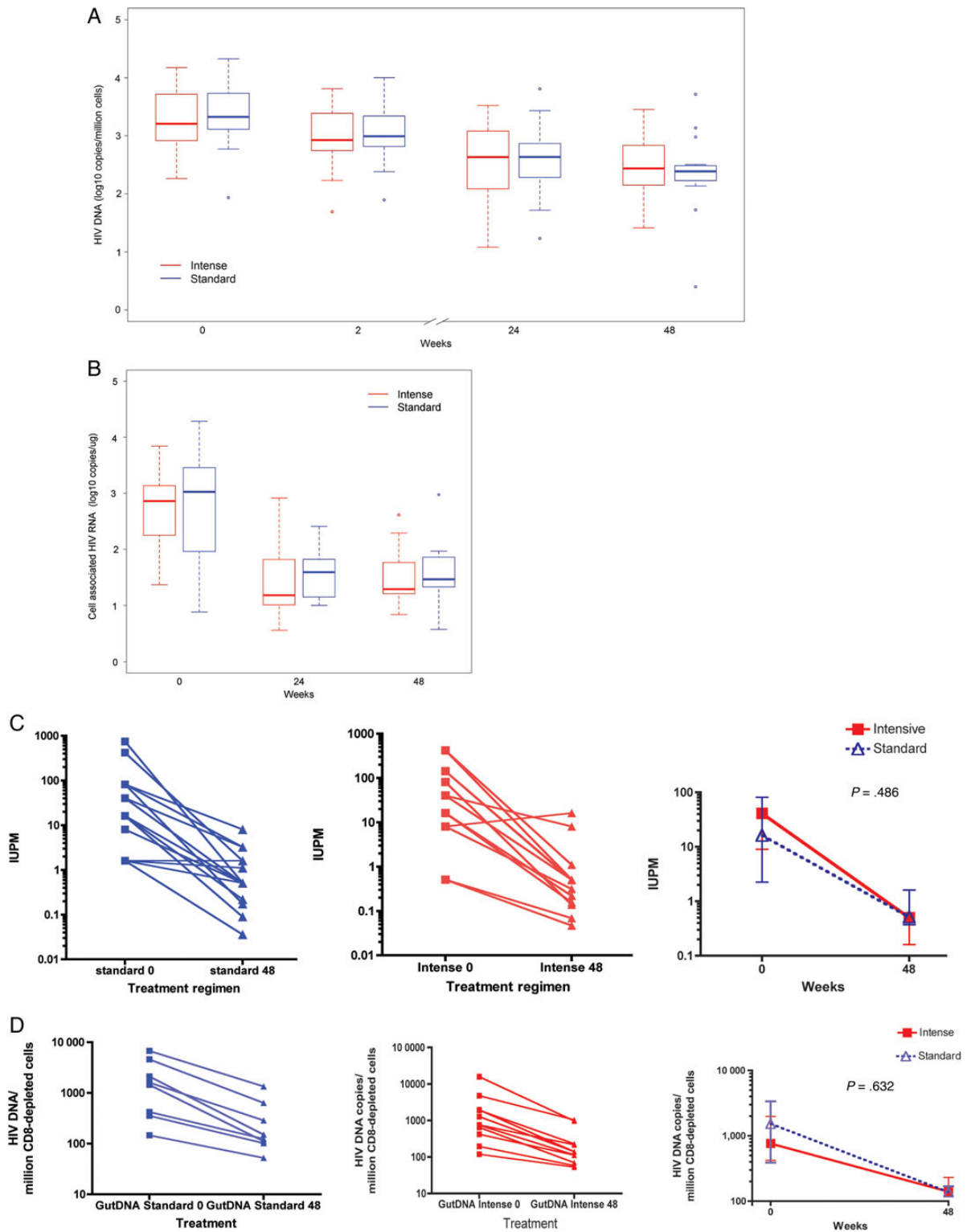
Figure 3. Human immunodeficiency virus (HIV) viral reservoir determinations for standard and intensive therapy groups. In (A) are kinetics of proviral DNA copies/million isolated CD4^{+} T cells from peripheral blood mononuclear cells (PBMC) (n = 30, medians with interquartile ranges); in (B) are baseline 24- and 48-week HIV RNA/μg of RNA from isolated CD4^{+} T cells from PBMC (n = 30, medians with interquartile ranges); in (C) are infectious HIV units cultured/million isolated CD4^{+} T cells from PBMC (n = 29 evaluable), with summary graph far right (medians with interquartile ranges); and in (D) are proviral DNA copies/million isolated CD8-depleted cells from sigmoid colon mononuclear cells (n = 19 evaluable), with summary graph far right (medians with interquartile ranges). Abbreviation: VL, viral load.
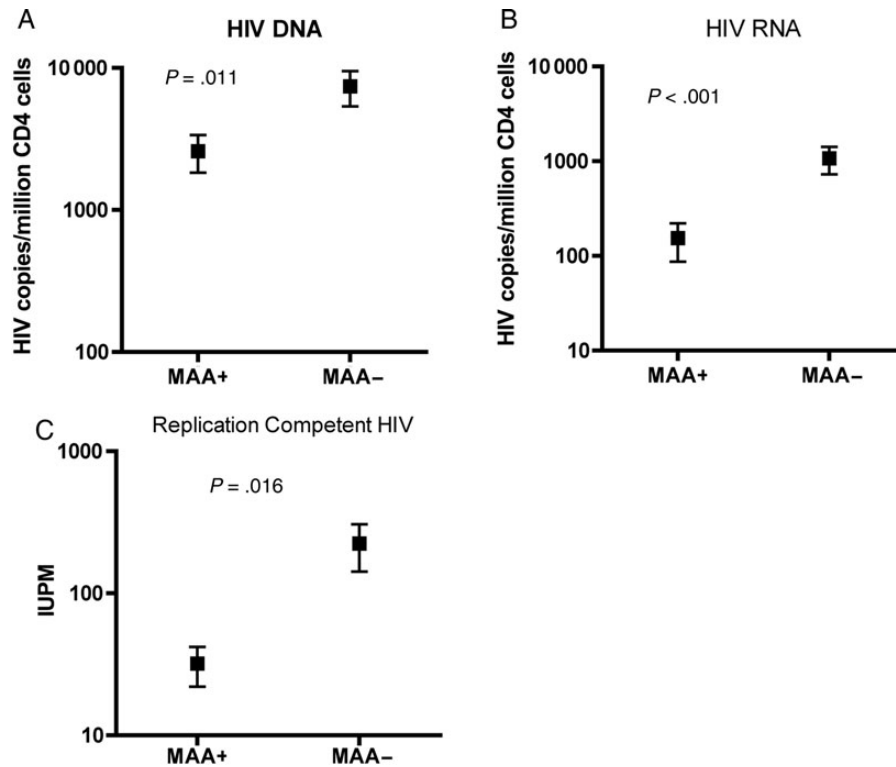
Figure 4. Human immunodeficiency virus (HIV) reservoirs correlate with recency of HIV infection. Reservoir determinations at baseline were stratified according to recent infection (<141 days) based on multiassay algorithm (MAA) or early infection (>141 days <6 months). Shown in (A) are HIV proviral DNA in peripheral blood mononuclear cells (PBMC), (B) HIV RNA in PBMC, in (C) replication competent HIV in PBMC by IUPM. *P* values based on 2-sample *t* test or Wilcoxon rank sum as appropriate.

DISCUSSION

In this pilot, randomized, blinded trial in early HIV infection, the institution of an intensive antiretroviral regimen that included a CCR5 inhibitor (maraviroc) and an integrase inhibitor (raltegravir) in addition to standard cART did not further reduce virus reservoirs in the peripheral blood or gut tissue after 1 year of treatment. Although the intensive regimen tended to have a more rapid antiviral effect, as reflected by the trends for more rapid clearance of plasma virus and lower CD4+ T cell-associated HIV RNA, this potential effect did not translate to any substantial reduction in persistent reservoirs, as measured by the rate of decay of proviral DNA or replication-competent virus cultures. Our findings are very similar to those by Markowitz et al [17] who also showed no difference in proviral DNA decay with an open-label, 5-drug regimen compared with a 3-drug regimen for 96 weeks and no differences in replication-competent virus from CD4+ T cells at 96 weeks. Furthermore, several studies have shown that 5-drug regimens are unable to reduce proviral burden when initiated during chronic HIV infection [18, 19].

Although HIV reservoir(s) are established early during the course of the infection, the size of the reservoir at this point is reduced compared with chronic infection, and so using treatment to eradicate the reservoir at this stage should theoretically be more feasible [7, 12]. In our cohort, we found that individuals captured early (MAA+) in infection had smaller reservoirs as determined by all assays measured. However, when we restricted our analysis to individuals who were MAA+, we still did not see any evidence that intensive therapy might reduce the reservoir more than a standard regimen. Of note, in the RV254/SEARCH 010 study in Thailand [20], an intensive cART regimen was associated with reduction of proviral DNA to undetectable levels in unfractionated PBMC in some individuals. However, that trial did not have a standard control arm, and so it is unclear whether those individuals would have responded differently with a standard regimen, or whether the observation was due to capturing individuals during Fiebig I stages when the reservoir is smaller.

One disadvantage of our study was that the majority of individuals were already Western blot positive (Fiebig IV), meaning that their reservoirs were already becoming established at presentation, and intensifying cART at this stage may be too little, too late. Nonetheless, our cohort is likely close to the "real-world" situation in the clinic with respect to treating early HIV infection, therefore highlighting the challenges of using
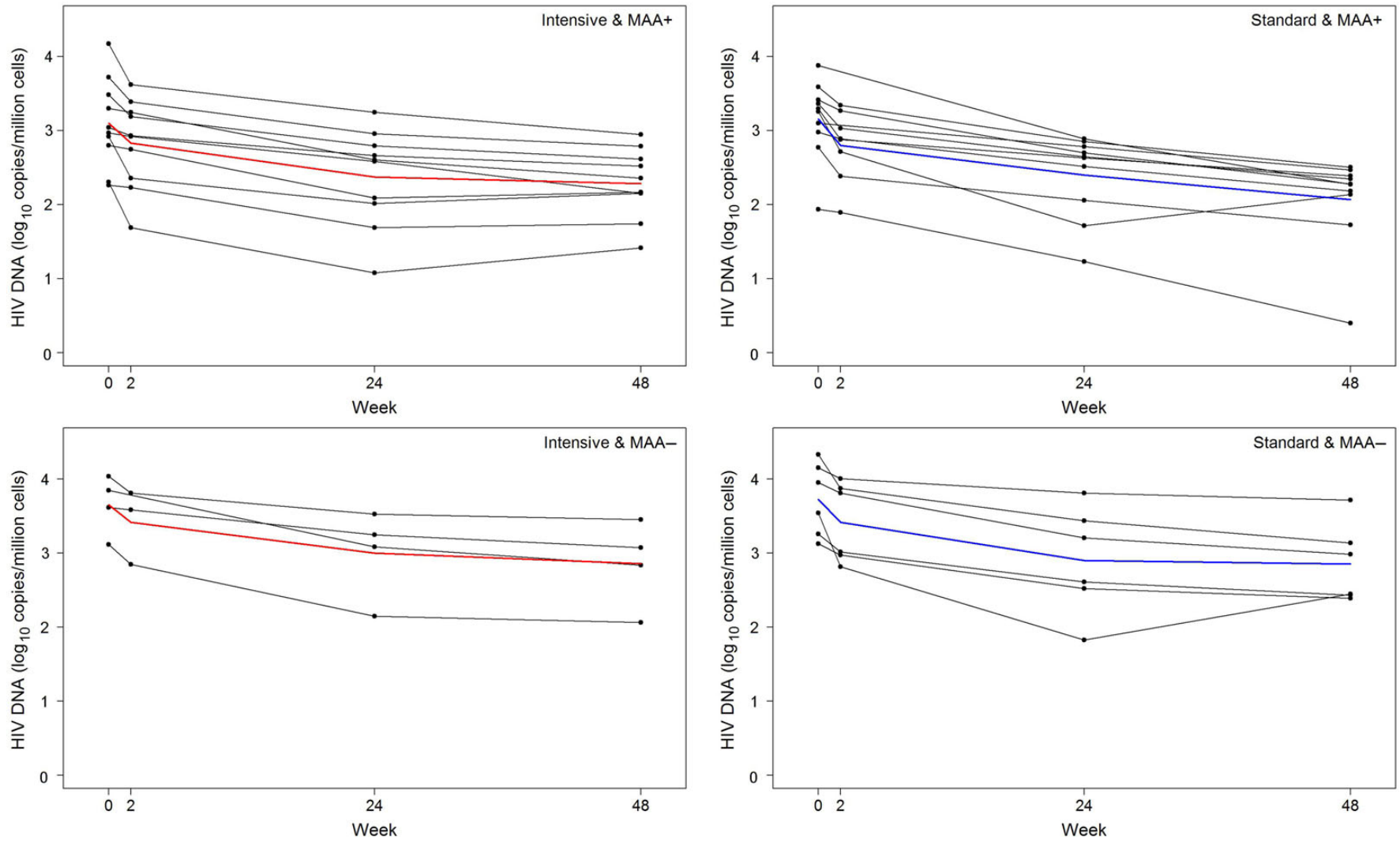
Figure 5. Peripheral blood mononuclear cell (PBMC) human immunodeficiency virus (HIV) proviral reservoirs in all subjects stratified according to multiassay algorithm (MAA) status and treatment group. The colored lines represent the means.

cART alone to reduce reservoirs. The relatively small sample size in this study is underpowered to detect smaller differences in reservoir sizes, which might be translated to greater differences over long-term follow up. Given that individuals with early/acute HIV infection are difficult to recruit in such clinical studies, future work incorporating multicenter trials will be necessary to obviate such limitations.

CONCLUSIONS

Our findings contribute to the mounting evidence that intensive antiretroviral regimens cannot impact HIV reservoirs above and beyond a standard regimen over the course of 1 year. Given the slow rate of decay of this reservoir, further studies are ongoing to determine whether a treatment effect is noticeable after a more prolonged treatment period (ie, >2 years). Our data also support the notion that cART regimens instituted during early HIV stages can reduce HIV reservoirs more rapidly than during chronic infection. In our study, standard and intensive cART reduced proviral and replication-competent virus by approximately 1 log, which is greater decay than seen during chronic infection treatment [12, 21]. It has recently been proposed that a >4 log reduction in the reservoir will be required to cure HIV infection [22]. Our data suggest that this will require novel strategies, such as virus reactivation and mobilization of the immune response [23], in addition to antiretroviral therapy.

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