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Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

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ABSTRACT

BACKGROUND

CCR5 is the major coreceptor for human immunodeficiency virus (HIV). We investigated whether site-specific modification of the gene ("gene editing") — in this case, the infusion of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN) — is safe.

METHODS

We enrolled 12 patients in an open-label, nonrandomized, uncontrolled study of a single dose of ZFN-modified autologous CD4 T cells. The patients had chronic aviremic HIV infection while they were receiving highly active antiretroviral therapy. Six of them underwent an interruption in antiretroviral treatment 4 weeks after the infusion of 10 billion autologous CD4 T cells, 11 to 28% of which were genetically modified with the ZFN. The primary outcome was safety as assessed by treatment-related adverse events. Secondary outcomes included measures of immune reconstitution and HIV resistance.

RESULTS

One serious adverse event was associated with infusion of the ZFN-modified autologous CD4 T cells and was attributed to a transfusion reaction. The median CD4 T-cell count was 1517 per cubic millimeter at week 1, a significant increase from the preinfusion count of 448 per cubic millimeter ($P<0.001$). The median concentration of *CCR5*-modified CD4 T cells at 1 week was 250 cells per cubic millimeter. This constituted 8.8% of circulating peripheral-blood mononuclear cells and 13.9% of circulating CD4 T cells. Modified cells had an estimated mean half-life of 48 weeks. During treatment interruption and the resultant viremia, the decline in circulating *CCR5*-modified cells (–1.81 cells per day) was significantly less than the decline in unmodified cells (–7.25 cells per day) ($P=0.02$). HIV RNA became undetectable in one of four patients who could be evaluated. The blood level of HIV DNA decreased in most patients.

CONCLUSIONS

CCR5-modified autologous CD4 T-cell infusions are safe within the limits of this study. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00842634.)

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The ability to make site-specific modifications to (or "edit") the human genome has been an objective in medicine since the recognition of the gene as the basic unit of heredity.[1,2] The challenge of genome editing is the ability to generate a single double-strand break at a specific point in the DNA molecule. Numerous agents, including meganucleases, oligonucleotides that form DNA triplexes, and peptide nucleic acids, have been tested and shown to be limited by inefficiency.[3-5] Another class of reagents, the zinc-finger nucleases (ZFNs), have proved versatile for genome editing, and the use of ZFNs is now well established in a number of model organisms and in human cells.[6,7]

ZFNs are well suited for genome engineering because they combine the DNA recognition specificity of zinc-finger proteins (ZFPs) with the robust but restrained enzymatic activity of the cleavage domain of the restriction enzyme *Fok*I (a nuclease).[6,7] ZFPs, which provide DNA-binding specificity, contain a tandem array of Cys_2His_2 zinc fingers, each recognizing approximately 3 base pairs of DNA.[8] By comparison, the bacterial type IIS restriction endonuclease, *Fok*I, has no sequence specificity and must dimerize to cut the DNA.[9] After the ZFN-mediated double-strand cut, the DNA can be repaired by either homologous recombination or nonhomologous end joining. Homologous recombination repairs the break while preserving the original DNA sequence. However, these cells are susceptible to recutting by ZFNs. In contrast, nonhomologous end joining can result in random insertion or deletion of nucleotides at the break site, resulting in permanent disruption of the primary DNA sequence. Therefore, nonhomologous end joining can be exploited to mutate a specific gene, leading to its functional knockout.[6,7]

The design of a ZFN pair consisting of two 4-finger proteins that bind to a target site within the human chemokine (C-C motif) receptor 5 gene (*CCR5*) was reported previously.[10] In preclinical tests, *CCR5*-modified CD4 T cells expanded and functioned normally in response to mitogens, were protected from human immunodeficiency virus (HIV) infection, and reduced HIV RNA levels in a humanized mouse model (involving xenotransplantation) of HIV infection.[10]

We selected *CCR5*, which encodes a coreceptor for HIV entry,[11,12] for several reasons. First, its disruption seemed likely to increase the survival of CD4 T cells; persons homozygous for a 32-bp deletion (delta32/delta32) in *CCR5* are resistant to HIV infection.[13] In vitro, CD4 T cells from such persons are highly resistant to infection with CCR5-using strains of HIV, which are the dominant strains in vivo.[14] Moreover, persons who are heterozygous for *CCR5* delta32 and who have HIV infection have a slower progression to the acquired immunodeficiency syndrome.[15,16] Furthermore, the effectiveness of blocking or inhibiting CCR5 with the use of small-molecule inhibitors has been shown in humans.[17] Finally, one person who underwent allogeneic transplantation with progenitor cells homozygous for the *CCR5*-delta32 deletion has remained off antiviral therapy for more than 4 years, with undetectable HIV RNA and proviral DNA in the blood, bone marrow, and rectal mucosa.[18,19] Although the mechanism responsible for the apparent cure associated with this procedure remains to be established, acquired CCR5 deficiency is one possibility.[20] Here we report the partial induction of acquired genetic resistance to HIV infection after targeted gene disruption (i.e., the infusion of autologous CD4 T cells modified at *CCR5* by a ZFN).

METHODS

We enrolled 12 patients in two case series (cohort 1 and cohort 2), each with 6 patients (Table 1). The patients had chronic aviremic HIV infection while they were receiving highly active antiretroviral therapy (HAART). Patients were infused with SB-728-T (Sangamo BioSciences), consisting of autologous CD4-enriched T cells that have been modified at the *CCR5* gene locus by ZFNs. The investigational ZFN was donated by Sangamo BioSciences, which had no role in any aspect of the study design, the writing of the manuscript, or the decision to submit the manuscript for publication; the ZFN-modified cells were manufactured at the University of Pennsylvania. The primary objective of the study was to assess the safety and side-effect profile of a single dose of autologous CD4-enriched T cells modified at *CCR5* by ZFNs. Secondary objectives included the assessment of increases in the CD4 T-cell count, persistence of the modified cells, homing to gut mucosa, and effects on viral load. Details of a concurrent control cohort are outlined in Table S3 in the Supplementary Appendix, available

Table 1. Patient Demographics and Cell Manufacturing.*

Cohort and Patient No.†	Age	Race or Ethnic Group	Sex	Duration of HIV Infection	Baseline CD4 T-Cell Count	Baseline CD4:CD8 T-Cell Ratio	SB-728-T Dose‡	SB-728-T CD3§	SB-728-T Cell Modification	SB-728-T Pentamer Duplication
	yr			*yr*	*per mm³*			%	%	*per 10⁶ cells*
Cohort 1										
201	54	White	M	20.2	665	1.38	1.00×10^{10}	97.0	14.6	57,000
203	50	Black	M	21.1	659	0.59	1.08×10^{10}	97.7	24.5	81,000
204	31	White	M	4.3	621	1.43	1.00×10^{10}	97.9	10.9	47,000
205	50	White	M	2.4	955	1.99	1.00×10^{10}	99.1	19.1	64,000
251	56	White	M	23.1	554	1.67	1.00×10^{10}	98.6	14.4	57,000
253	38	Asian	M	2.8	997	0.98	1.00×10^{10}	94.3	18.4	61,000
Median	50			12.3	662	1.41	1.00×10^{10}	97.8	16.5	59,000
Cohort 2										
306	50	White	M	19.1	271	0.99	0.77×10^{10}	93.1	20.9	60,000
308	37	Black	M	13.1	328	0.78	0.50×10^{10}	97.5	25.3	67,000
309	48	Asian Indian	F	2.9	341	0.54	0.80×10^{10}	92.3	27.7	67,000
351	60	Black	M	14.1	193	1.25	1.00×10^{10}	97.7	25.4	73,000
354	41	Hispanic	M	15.6	220	0.50	0.90×10^{10}	99.3	26.7	69,000
355	44	Black	F	16.2	272	0.65	1.00×10^{10}	94.1	26.9	72,000
Median	46			14.9	272	0.72	0.85×10^{10}	95.8	26.0	68,000

* SB-728-T consists of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by zinc-finger nucleases.
† Cohort 1 comprised patients with adequate CD4 T-cell recovery after highly active antiretroviral therapy (HAART), defined as those with CD4 T-cell counts above 450 per cubic millimeter at screening, with a documented nadir of not lower than 300 per cubic millimeter. Cohort 2 comprised patients with inadequate CD4 T-cell recovery after HAART, defined as those with CD4 T-cell counts persistently between 200 per cubic millimeter and 500 per cubic millimeter at screening, despite 2 or more years of HAART.
‡ A single dose of autologous CD4 T cells modified at *CCR5* by SB-728-T consisted of an infusion of a median of 1.00×10^{10} total cells in cohort 1, and a median of 0.85×10^{10} in cohort 2.
§ The percentages of total cells expressing the T-cell marker CD3 are listed.

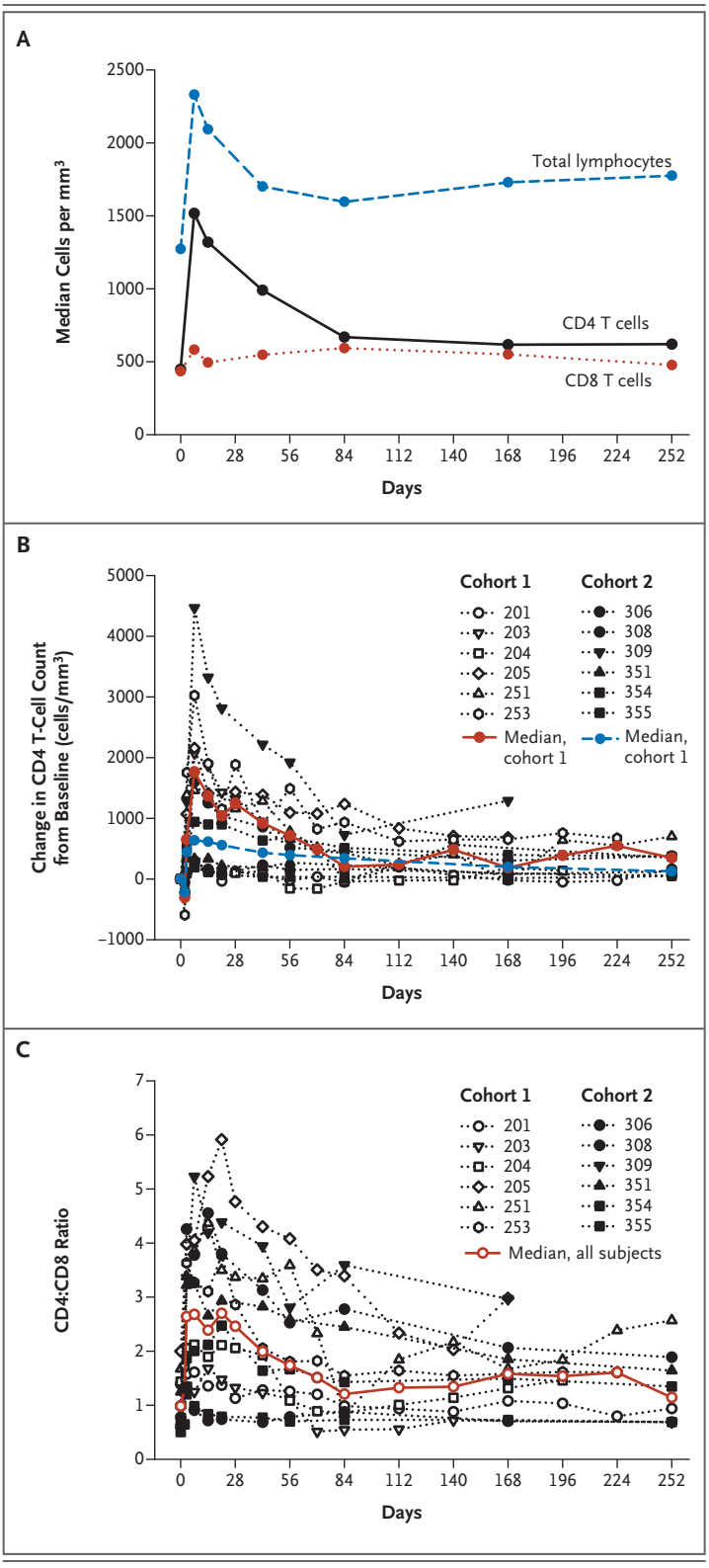

Figure 1. Lymphocyte Values.

In Panel A, median total lymphocyte, CD4 T-cell, and CD8 T-cell values for all study participants are shown (see Fig. S1 in the Supplementary Appendix). The increase in total lymphocyte count is due to an increase in the number of CD4 T cells, since changes in CD8 counts are negligible. In Panel B, the change in CD4 T-cell count from baseline is plotted for all participants, and the median change is plotted for each cohort. In Panel C, the median ratios of CD4 T cells to CD8 T cells are plotted for all participants.

with the full text of this article at NEJM.org. Details of the methods and the statistical analysis are provided in the Supplementary Appendix. All patients provided written informed consent. All the authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol.

RESULTS

ADVERSE EVENTS

One serious adverse event occurred in a single patient from cohort 2. Fever, chills, joint pain, and back pain developed in the patient and precipitated a visit to the emergency department within 24 hours after infusion of the study drug. We attributed the symptoms to a transfusion reaction related to the study drug (see the Supplementary Appendix for further details).

CHANGES IN CIRCULATING LYMPHOCYTES

The median total lymphocyte counts within the vascular compartment significantly increased in the 12 patients, from 1.27×10^3 per cubic millimeter at baseline to 2.33×10^3 per cubic millimeter 1 week after the infusion of SB-728-T ($P=0.002$ with the use of a sign test) (Fig. 1A). Subsequently, the median circulating lymphocyte count progressively declined to 1.70×10^3 per cubic millimeter by 6 weeks and was stable thereafter (1.60×10^3, 1.73×10^3, and 1.78×10^3 per cubic millimeter at 12, 24, and 36 weeks, respectively). The increase in CD8 T-cell counts was moderate, with a median of 435 per cubic millimeter at baseline as compared with 582 per cubic millimeter at week 1. By comparison, the CD4 T-cell counts in these patients significantly increased, from a median of 448 per cubic millimeter at baseline to

1517 per cubic millimeter at week 1 (P<0.001 with the use of a sign test) (Fig. 1A, and Fig. S1 in the Supplementary Appendix). All patients had increased CD4 T-cell counts after infusion (Fig. 1B, and Tables S1 and S2 in the Supplementary Appendix), but we observed heterogeneity between participants in both cohorts, with most of the increase in CD4 T-cell counts derived from 7 participants who had large increases in CD4 T-cell counts. Median changes in CD4 T-cell count from baseline, according to cohort, are shown in Figure 1B. We observed a median (±SD) increase of 1201±1350 cells per cubic millimeter at week 1 that progressively declined to a median of 615 cells per cubic millimeter at the end of 36 weeks but remained above the baseline levels by 256 cells per cubic millimeter (Fig. 1B, and Fig. S1 in the Supplementary Appendix). The median increase in CD4 T-cell count at week 1 was 1765±1138 per cubic millimeter in participants with adequate CD4 T-cell recovery after HAART (sometimes referred to as immune responders, defined as those with CD4 T-cell counts >450 per cubic millimeter at screening, with a documented nadir of not lower than 300 per cubic millimeter) and 637±1638 per cubic millimeter in participants with inadequate CD4 T-cell recovery after HAART (sometimes referred to as immune nonresponders, defined as those with CD4 T-cell counts persistently between 200 per cubic millimeter and 500 per cubic millimeter at screening, despite ≥2 years of HAART), but the difference between the two groups was not significant (P=0.75 by the Mann–Whitney test). A finding consistent with these observations was that the median ratio of CD4 T cells to CD8 T cells more than doubled, from 0.99 at baseline to 2.62 at week 1 (Fig. 1C); the median ratio declined to 1.14 by week 36.

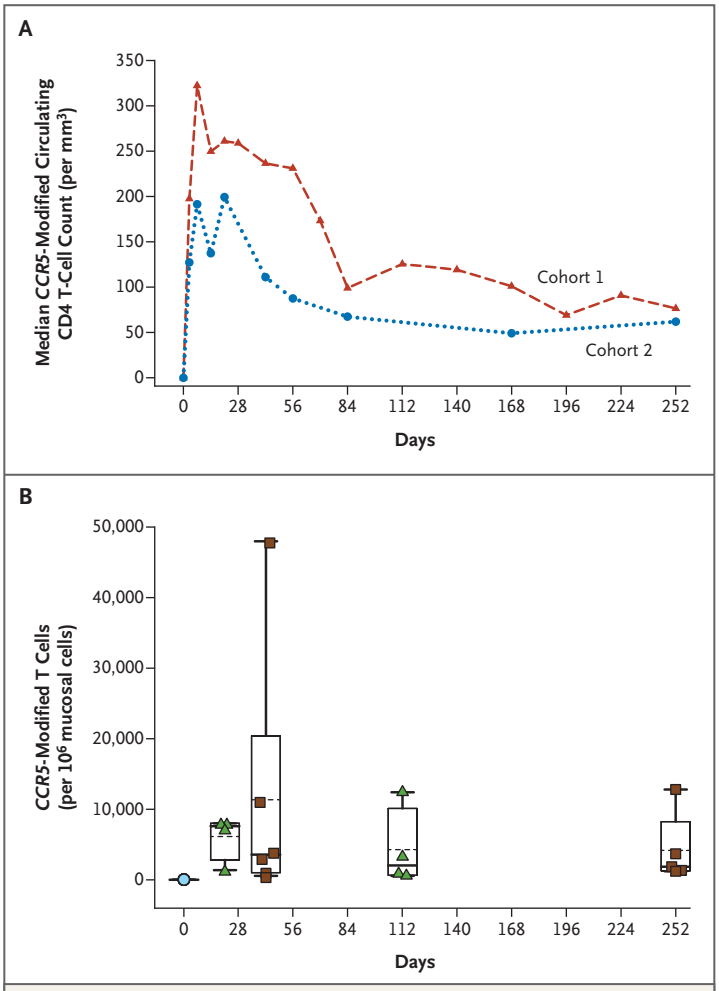

Figure 2. *CCR5*-Modified CD4 T Cells in the Circulation and Mucosal Tissues.
Panel A shows that the median absolute number of *CCR5*-modified circulating CD4 T cells was similar in participants with adequate CD4 T-cell recovery after highly active antiretroviral therapy (HAART) (cohort 1) and in those with inadequate CD4 T-cell recovery after HAART (cohort 2). Panel B shows *CCR5*-modified cell traffic to rectal mucosal tissues. Patients in cohort 1 (green triangles) underwent a rectal biopsy at baseline (blue circle) and on days 21 and 112, and those in cohort 2 (brown squares) underwent biopsies at baseline (blue circle) and on days 42 and 252. Box plots show the 25th percentile (lower edge of the box), mean (dotted line in the box), median (solid line in the box), 75th percentile (upper edge of the box), and 90th percentile (whisker). *CCR5*-modified CD4 T-cells constituted a mean of 0.6%, 1.1%, 0.4%, and 0.4% (and a median of 0.8%, 0.4%, 0.2%, and 0.2%) of rectal mucosal mononuclear cells on days 21, 42, 112, and 252, respectively.

ENGRAFTMENT OF *CCR5*-MODIFIED CD4 T CELLS

CCR5-modified CD4 T cells could be tracked after infusion because of the creation of a five-nucleotide (pentamer) duplication that occurred in approximately 25% of the modified cells.[10] Therefore, the total number of gene-modified cells is calculated by multiplying the number of cells with the pentamer duplication by four (see the Supplementary Appendix). After infusion, we observed an increase in the number of *CCR5*-modified circulating CD4 T cells (Fig. 2A), with peak levels observed at week 1 (range among the 12 patients, 30 to 1106 cells per cubic millimeter). The median concentration of *CCR5*-modified

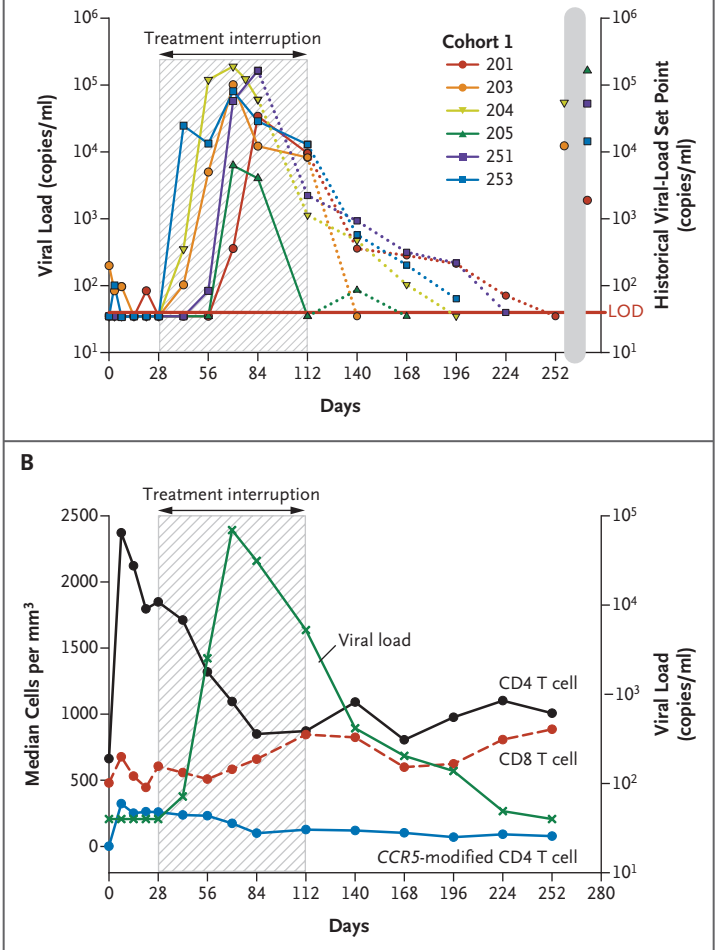

Figure 3. Changes in Viremia during Treatment Interruption.

Panel A depicts HIV viral loads (HIV RNA) for the six patients in cohort 1. SB-728-T was infused on day 0. A 12-week (84-day) treatment interruption (shaded area) was initiated on day 28 and terminated on day 112. The treatment interruption was terminated prematurely, on day 84 (week 8 of the interruption period), in Patients 204 and 251. The dotted lines indicate reinstitution of highly active antiretroviral therapy. The historical HIV-RNA set point for each patient is also shown. The limit of detection (LOD) for the viral-load assay is plotted at 50 copies. Patient 205 was heterozygous for *CCR5* delta32. Panel B shows the median CD4 T-cell, CD8 T-cell, and *CCR5*-modified T-cell counts in cohort 1 during the treatment interruption, as well as the viral load.

CD4 T cells at 1 week was 250 cells per cubic millimeter. This constituted a median of 8.8% of peripheral-blood mononuclear cells (PBMCs) and 13.9% of the CD4 T cells in the vascular compartment (Fig. S2 in the Supplementary Appendix). The number of *CCR5*-modified CD4 T cells in the circulation constituted a similar percentage of the circulating CD4 T cells and PBMCs in the participants with and in those without adequate CD4 T-cell recovery after HAART (Fig. S2 in the Supplementary Appendix). The time to peak level (known as T_{max}) of gene-modified cells ranged from 3 to 14 days (median, 7). The number of gene-modified cells in the vascular compartment decreased moderately, with an estimated mean half-life of 48 weeks at a median follow-up of 64 weeks (range, 24 to 142). The gene-modified T cells could be detected in all patients at all subsequent time points examined during the long-term follow-up study, the longest to date being 42 months in the first patient, at which time *CCR5*-modified CD4 T cells were present at a concentration of 13 cells per cubic millimeter, representing 0.6% of circulating PBMCs and 1.7% of circulating CD4 T cells, respectively.

TRAFFICKING OF *CCR5*-MODIFIED CD4 T CELLS TO RECTAL MUCOSA

In humans, the vascular compartment contains 1 to 2% of the T-cell mass, whereas the mucosal tissues are the largest lymphoid reservoir, containing at least 50% of the T-cell mass.[21] In this study, *CCR5*-modified CD4 T cells were detected in all rectal-biopsy specimens. One patient in cohort 1 declined to undergo the scheduled biopsies; the remaining 11 participants underwent biopsies on two or more occasions. A total of 30 of 33 scheduled biopsies were performed. Gene-modified cells constituted a median of 0.8% of rectal mononuclear cells on day 21 and varied from 0.4% to 0.2% thereafter (Fig. 2B).

TREATMENT INTERRUPTION

Participants in cohort 1 underwent a 12-week interruption in treatment that began 4 weeks after SB-728-T infusion. Viral load, as measured by HIV RNA, was below the limit of detection in all six patients at the start of the treatment interruption. Viral load became detectable in four of the six patients (66.7%) 2 to 4 weeks after the cessation of HAART and peaked at 6 to 8 weeks. The treatment interruption was terminated prematurely, at 8 weeks, in Patient 204 and Patient 251 (Fig. 3A). In Patient 204, HAART was reinitiated because of three consecutive HIV RNA values exceeding 100,000 copies per milliliter, which was a prospectively defined stopping rule. In Patient 251, HAART was reinitiated because the patient's primary provider was concerned about the rapid increase in the viral load. In the four patients

who completed the 12-week treatment interruption, the viral load decreased during the interruption by an average of 1.2 $\log_{10}$ (range, 0.5 to 2.1) from the peak level during the absence of HAART (P=0.07). Patient 205, who had a pretreatment viral set point of 165,000 copies per milliliter and who we later discovered is heterozygous for *CCR5* delta32, did not show an increase in viral load until week 6 of the treatment interruption, at which time the viral load peaked at 6247 copies per milliliter, a value below the set point. The viral load in this patient declined thereafter and was below the limit of detection before reinstitution of HAART.

In cohort 1, the median circulating CD4 T-cell count changed from 1849 per cubic millimeter (range, 720 to 2881) at the onset of the treatment interruption to 1711 per cubic millimeter (range, 719 to 2341) at the onset of viremia (after 2 weeks of treatment interruption) (P=0.38). Relative to the start of the interruption, at week 4, the median CD4 T-cell count continued to decline, to 1095 per cubic millimeter at the peak of viremia, at week 10 (P=0.06) (Fig. 3B). At the end of the 12-week treatment interruption, the median CD4 T-cell count was 872 per cubic millimeter; the median decrease from the start of the interruption was 237±315 cells per cubic millimeter (P=0.69). Similarly, the median number of circulating *CCR5*-modified CD4 T cells declined from 259 per cubic millimeter at the onset of treatment interruption to 126 per cubic millimeter at the end of the treatment interruption (P=0.03), with a median decrease of 126±76 cells per cubic millimeter. Concomitant with HIV replication, the median CD8 T-cell count, which had been 605 per cubic millimeter at the start of the treatment interruption, peaked at 845 per cubic millimeter at the end of the treatment interruption, at week 16 (P=0.69).

Thereafter, with the resumption of antiretroviral treatment, the median CD8 T-cell count decreased to pre–treatment-interruption levels at week 24, and the median CD4 T-cell count progressively increased to 1007 per cubic millimeter by the end of the 36-week study. The kinetics of the decline in *CCR5*-modified CD4 T cells and in unmodified CD4 T cells may differ (Fig. 4A). With the use of mixed quantile regression, the rate of decline during the treatment interruption was significantly greater for the median unmodified CD4 T cells (–7.25 cells per day; 95% confidence interval [CI], –12.14 to –2.94) than for the *CCR5*-modified CD4 T cells (–1.81 cells per day; 95% CI, –3.08 to –0.46) (P=0.02). However, the difference in the decline for the mean cell counts over time did not reach significance when they were compared by means of a linear mixed-effects model (P=0.08).

To further assess the safety of the infusions and treatment interruption, we also measured HIV DNA in the patients' PBMCs by droplet digital polymerase-chain-reaction (PCR) assay, which is more sensitive by a factor of approximately 100 than are conventional assays.[22] Despite an approximate 3-$\log_{10}$ increase in the mean HIV-RNA copy number in the plasma, the HIV DNA level did not change in five patients during treatment interruption, was significantly increased in one patient during the treatment interruption, and returned to baseline in all six patients after the resumption of antiretroviral treatment (Fig. S3 in the Supplementary Appendix).

We also assayed the number of copies of *gag*, a gene encoded by HIV DNA, in the peripheral blood of participants in cohort 2 (Fig. S4 in the Supplementary Appendix). The *gag* levels decreased in four patients, remained stable in one patient, and were below the limit of detection in one patient. Using the same assay, we assessed the rates of HIV DNA decay in a series of aviremic patients (i.e., those with an undetectable level of HIV RNA [<75 copies per milliliter], according to ultrasensitive PCR assay) who did not receive SB-728 T-cell infusions (Table S3 in the Supplementary Appendix). The demographics of these patients are similar to those in cohorts 1 and 2. The rates of HIV DNA decline in the concurrent control cohort are shown in Figures S5 and S6 in the Supplementary Appendix. A comparison of the median and mean changes in *gag* copies indicates that the rate of HIV DNA decline is approximately 10 times as rapid in the cohort 2 patients as in the aviremic control cohort, although the difference in slopes was not significant (P=0.65) (Table S4 in the Supplementary Appendix).

DISCUSSION

In this study, we tested the safety and feasibility of inducing acquired genetic resistance to HIV infection in an attempt to mimic the known inherited resistance displayed by persons with the

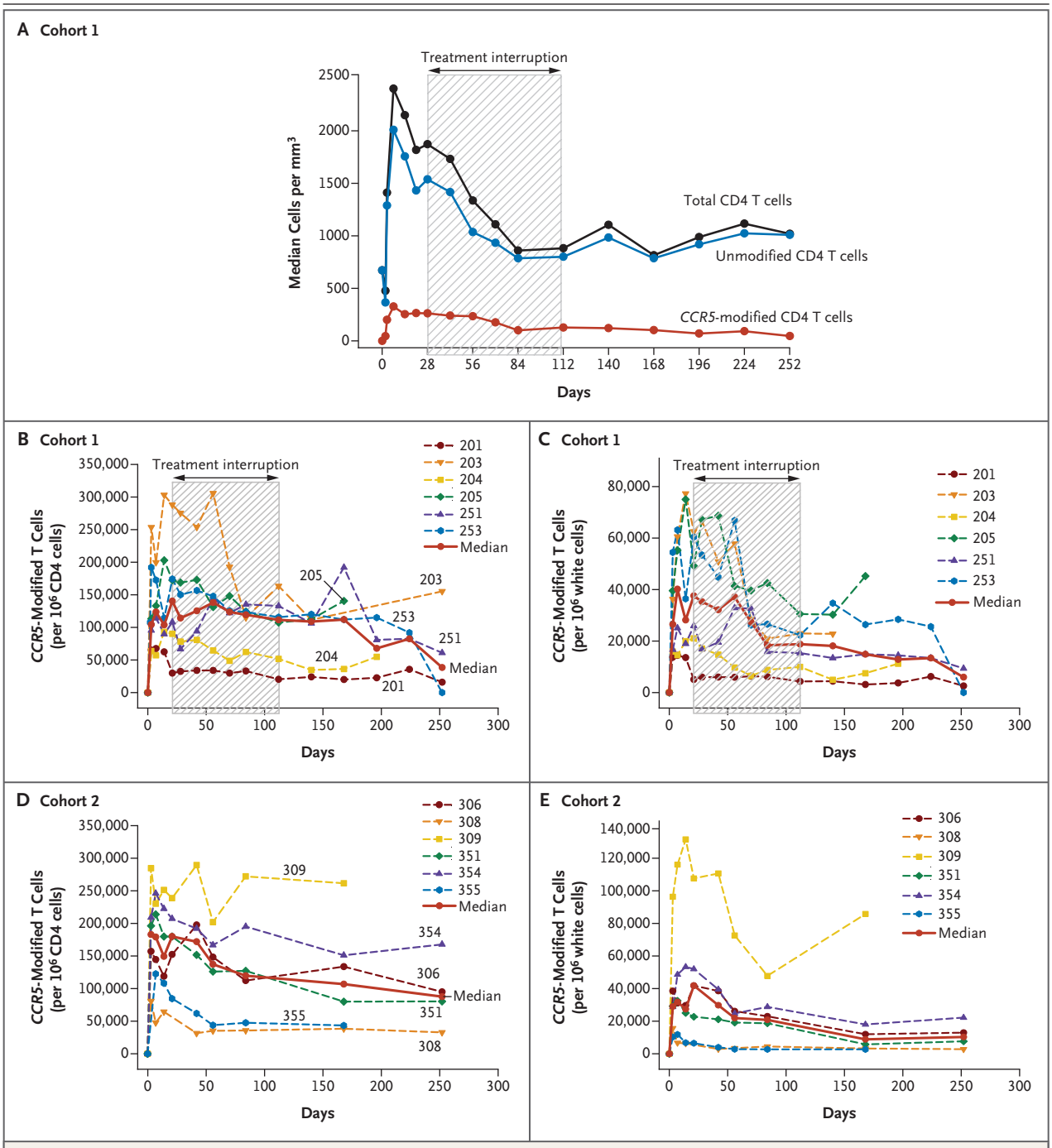

Figure 4. *CCR5*-Modified CD4 T Cells during Treatment Interruption.

The median count for total CD4 T cells, unmodified CD4 T cells, and *CCR5*-modified CD4 T cells for all patients in cohort 1 is plotted in Panel A. *CCR5*-modified CD4 T cells in blood are shown as a fraction of CD4 cells (Panels B and D) and as a fraction of white cells (Panels C and E).

CCR5-delta32 mutation.[13,15,16] The infusion of autologous CD4 T cells in which the CCR5 receptor had been rendered dysfunctional by ZFNs targeting *CCR5* was generally safe, although the small cohort sizes in the study render null the generalizability of this conclusion. The gene-

modified cells readily engrafted and persisted after adoptive transfer. Potential beneficial effects associated with the infusion of SB-728-T included increased levels of CD4 T cells. The observed relative survival advantage of the gene-modified cells during treatment interruption suggests that genome editing at the *CCR5* locus confers a selective advantage to CD4 T cells in patients infected with HIV.

The long-term persistence of the *CCR5*-modified CD4 T cells suggests that the cells were not rendered immunogenic as a result of *CCR5* disruption. Immune deficiency is unlikely to explain the lack of rejection of the *CCR5*-modified cells, because previous studies have shown that gene-modified T cells engineered with immunogenic viral vectors can be rapidly eliminated by immune-mediated clearance in patients with late-stage HIV.[23] Although the persistence of *CCR5*-modified cells as measured by the concentration in blood is similar in the two cohorts, the percentage of *CCR5*-modified CD4 T cells appears to be more stable than does the concentration of unmodified CD4 T cells in the blood, suggesting differential rates of cell death or trafficking to extravascular compartments. The decline in *CCR5*-modified CD4 T cells in the PBMC compartment may reflect, at least in part, egress from the vascular compartment and accumulation in the mucosal immune system. Since the vascular compartment contains only 1 to 2% of the T-cell mass, it is possible that the total body content of *CCR5*-modified cells is underestimated by the counts in the blood compartment, given the presence of *CCR5*-modified cells in the rectal mucosa and the large size of the mucosal immune component.[21]

The study participant with the longest delay in viral recrudescence was later discovered to be heterozygous for the *CCR5* deletion. Preliminary analyses suggest that the degree of biallelic disruption of *CCR5* may correlate with control of viral load (Fig. S7 in the Supplementary Appendix). Successful clinical application will most likely depend on biallelic knockout in persons who have two nonmutated *CCR5* alleles.

We have applied the principles of synthetic biology[24] to the goal of creating an immune system that is resistant to HIV infection. Our strategy is to repopulate the immune system with CCR5-deficient central memory T lymphocytes by infusion of SB-728-T. Alternative approaches that are promising include infusions of autologous *CCR5*-modified hematopoietic stem cells,[25] stem-cell transplantation procedures, and the use of CCR5-specific ribozymes and short hairpin RNA.[26-28] We anticipate that our strategy will elucidate the contribution of acquired CCR5 deficiency to the antiviral effect that led to the functional eradication of HIV after *CCR5*-delta32 stem-cell transplantation.[18,19]

Our study supports the feasibility of targeted genome editing to introduce a disease-resistance allele. Future studies directed toward increasing the engraftment of these gene-modified cells are warranted.

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