

## HIV

# Coexistence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic controller

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Some HIV-1-infected patients develop broad and potent HIV-1 neutralizing antibodies (bNAbs) that when passively transferred to mice or macaques can treat or prevent infection. However, bNAbs typically fail to neutralize coexisting autologous viruses due to antibody-mediated selection against sensitive viral strains. We describe an HIV-1 controller expressing HLA-B57\*01 and HLA-B27\*05 who maintained low viral loads for 30 years after infection and developed broad and potent serologic activity against HIV-1. Neutralization was attributed to three different bNAbs targeting nonoverlapping sites on the HIV-1 envelope trimer (Env). One of the three, BG18, an antibody directed against the glycan-V3 portion of Env, is the most potent member of this class reported to date and, as revealed by crystallography and electron microscopy, recognizes HIV-1 Env in a manner that is distinct from other bNAbs in this class. Single-genome sequencing of HIV-1 from serum samples obtained over a period of 9 years showed a diverse group of circulating viruses, 88.5% (31 of 35) of which remained sensitive to at least one of the temporally coincident autologous bNAbs and the individual's serum. Thus, bNAB-sensitive strains of HIV-1 coexist with potent neutralizing antibodies that target the virus and may contribute to control in this individual. When administered as a mix, the three bNAbs controlled viremia in HIV-1<sub>YU2</sub>-infected humanized mice. Our finding suggests that combinations of bNAbs may contribute to control of HIV-1 infection.

## INTRODUCTION

A fraction of HIV-1-infected individuals develop broadly neutralizing antibodies (bNAbs) that show potent neutralizing activity against a range of different HIV-1 isolates (1–4). bNAbs typically develop over a period of 1 to 3 years during which time there is coevolution of circulating viral strains and antibodies (5–9). Virus and antibody coevolution starts when the infecting virus elicits early antibody responses that exhibit some levels of autologous neutralization (6, 9–11). These early antibodies put pressure on the virus and spur HIV-1 evolution. Viral strains that are sensitive to the antibodies are subjected to negative selection, resulting in the emergence of antibody-resistant HIV-1 variants that are subsequently targeted by coevolving antibody variants (5–7, 9, 12).

The bNAbs that emerge have high levels of somatic mutations, suggesting that B cells that produce bNAbs develop by iterative rounds of antibody gene mutation and selection in germinal centers (2, 5, 6, 13–17). The end result of serial antibody and HIV-1 mutation

is bNAbs that neutralize large numbers of heterologous viral variants but normally fail to neutralize autologous circulating viral strains (2, 6–9). Therefore, it is believed that bNAbs that develop during chronic infection are unable to control HIV-1 in the individual who develops them.

To reexamine the question of whether autologous bNAbs can coexist with bNAB-sensitive viruses and contribute to HIV-1 control, we studied an HLA (human leukocyte antigen)–B57\*01 HIV-1 controller (18, 19) who developed elite levels of HIV-1 neutralizing activity and maintained low levels of HIV-1 viremia for several years. Here, we describe the neutralizing antibodies that developed in this donor, the coexisting plasma viruses, and show that when combined, these bNAbs can suppress HIV-1 replication and maintain low-level viremia in vivo in HIV-1-infected humanized mice.

## RESULTS

### Multiple bNAbs isolated from donor EB354

Donor EB354 was diagnosed with HIV-1 clade B in 1986. Purified immunoglobulin G (IgG) from donor EB354 was first tested for neutralization in 2006 when the viral load was <400 copies/ml (Fig. 1, A and B, and table S1). The neutralizing activity increased between 2006 and 2010, and has remained broad and potent since that time (Fig. 1B). To isolate the antibodies that account for this subject's serologic activity, we sorted single IgG<sup>+</sup> B cells (20–22) using four different HIV-1 baits in four separate sorts: 2CC core (23), gp140<sub>YU2</sub> (24), a 1:1 mixture of gp140<sub>92UG37.8</sub> (clade A) + gp140<sub>CZA79012</sub> (clade C) (25), and BG505 SOSIP.664 (26). A total of 241 paired heavy and light chains were isolated, of which 152 antibodies formed 22 different clones (fig. S1A).

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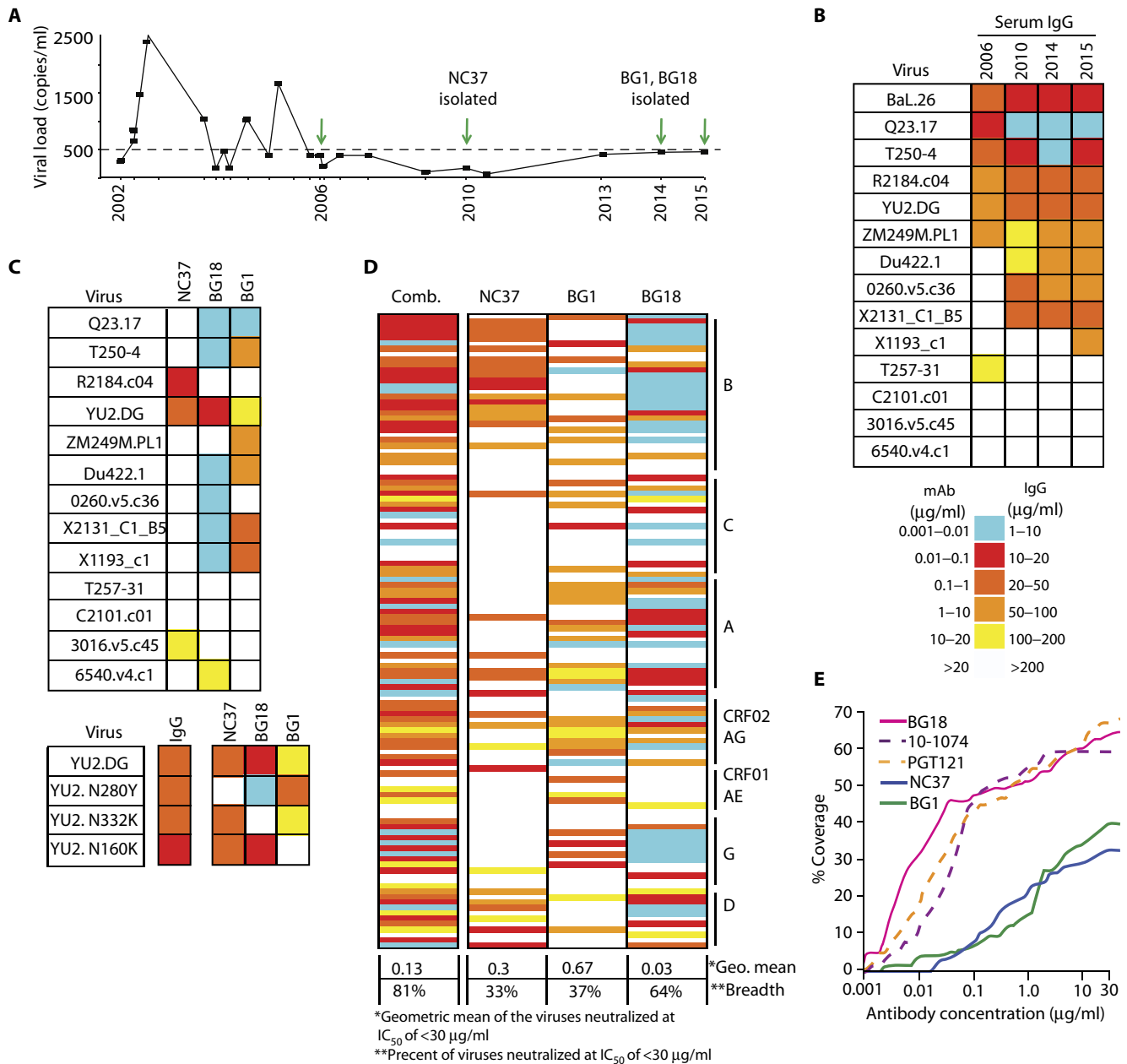
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**Fig. 1. Neutralizing antibodies isolated from donor EB354.** (A) Viral load values as measured in 2002 to 2015. The neutralizing antibodies were isolated when indicated. Plasma was collected at time points marked with green arrows. (B) Heat map showing the median inhibitory concentration (IC<sub>50</sub>) values (µg/ml) in TZM-bl assay of serum IgG from four time points [shown in (A)] tested against a panel of HIV-1 pseudoviruses. The color scheme is indicated below. mAb, monoclonal antibody. (C) Top: Heat map showing neutralization potency [as in (B)] for NC37, BG1, and BG18. Bottom: Neutralization potency of the donor IgG from 2014, as well as NC37, BG1, and BG18 against YU2<sub>WT</sub>, YU2<sub>N280Y</sub>, YU2<sub>N332K</sub>, and YU2<sub>N160K</sub>. (D) Heat map showing neutralization potency [as in (B)] of NC37, BG1, BG18 and a 1:1:1 combination (comb.) tested against a panel of 120 tier 2 HIV-1 pseudoviruses. The geometric mean of all neutralized viruses and the percent breadth are indicated in the bottom panel. All neutralization assays were performed in duplicate. (E) Coverage curve based on the values in table S2.

Antibodies from three clones showed tier 2 neutralizing activity: BG18, BG1, and NC37 (Fig. 1C and fig. S1B). Antibody BG18 (V<sub>H</sub>4-4 and V<sub>L</sub>3-25) recapitulated most of the serologic activity, whereas antibodies NC37 (V<sub>H</sub>1-46/1-2, V<sub>K</sub>3-20) and BG1 (V<sub>H</sub>3-49 and V<sub>K</sub>1-49) were less potent but complemented the activity of BG18 (Fig. 1C and fig. S1B).

To map the binding sites of the three neutralizing clones, we performed TZM-bl assays using HIV-1<sub>YU2</sub> variants carrying epitope-specific point mutations in Env. Whereas the polyclonal IgG from

the donor showed no measurable change in sensitivity to the mutants, antibody BG18 was sensitive to YU2<sub>N332K</sub> (glycan-V3), antibody BG1 to YU2<sub>N160K</sub> (V1V2), and antibody NC37 to YU2<sub>N280Y</sub> (CD4bs) (Fig. 1C, bottom). Our epitope mapping was confirmed by competitive enzyme-linked immunosorbent assay (ELISA) (for BG18 and BG1; fig. S2) and by a 2.7 Å resolution crystal structure of NC37 Fab bound to a gp120 core (fig. S3). We conclude that BG18 recognizes the glycan patch associated with the V3 loop, that

BG1 is specific for the V1V2 loops at the top of the molecule, and that NC37 is a CD4bs-specific antibody.

NC37 was isolated from a sample obtained in 2010, whereas BG1 and BG18 were isolated from peripheral blood mononuclear cells (PBMCs) collected in 2014. We examined available PBMCs from 2010 and 2013 using polymerase chain reaction (PCR) primers specific for BG1 and BG18. Whereas BG1 transcripts were detected at both time points, BG18 was first detected in 2013 and was not detected in 2010. We conclude that BG18 emerged between 2010 and 2013, whereas BG1 and NC37 developed earlier.

BG18 neutralized 64% of viruses in a 118-virus panel (Fig. 1D) with a geometric mean  $IC_{50}$  of 0.03  $\mu\text{g/ml}$ . Antibodies NC37 and BG1 showed geometric mean  $IC_{50}$  of 0.3 and 0.67  $\mu\text{g/ml}$  and 33 and 37% breadth, respectively (Fig. 1, D and E, and table S2). The 1:1:1 mix of the three bNAbs neutralized 81% of the viruses in the 118-virus panel with a geometric mean  $IC_{50}$  of 0.130  $\mu\text{g/ml}$ , indicating an additive effect (Fig. 1D, left column, and table S3).

BG18 is comparable to PGT121 and 10-1074, two previously isolated potent bNAbs directed against the base of the V3 region of Env (27, 28), in terms of its breadth of coverage, but BG18 is more potent (Fig. 1E and table S2). The germline genes of BG18 and PGT121/10-1074 ( $V_{H4-4}$  and  $V_{H4-59}$ , respectively) are closely related (~90% identity); however, the mature heavy chains of BG18 and PGT121/10-1074 are only about 62% identical. The light chains of BG18 and PGT121/10-1074 are more distinct (70% identity for germ lines and ~48% identity for the mature antibodies) (Fig. 2, A and B, and fig. S4). BG18 is more mutated than PGT121/10-1074; however, it does not contain any insertions or deletions, which were reported for members of PGT121/10-1074 (27). On a structural level, we found four key differences between PGT121/10-1074 and BG18. First, as revealed by the 1.3 Å resolution crystal structure of the BG18 Fab, the CDRH3 of BG18 folds on itself instead of extending fully as in PGT121/10-1074 (Fig. 2C, left, and table S5). This conformation of CDRH3<sub>BG18</sub> is stabilized by hydrogen bonds. Second, as expected from the sequence alignment, the  $V_L$  domain of BG18 differs in its orientation from PGT121/10-1074 (root mean square deviations of 3.1 Å were found for superimposing 93 or 92 C $\alpha$  atoms in comparison to light chains in BG18-PGT121 and BG18-10-1074 superimpositions, respectively; Fig. 2C, right). Third, BG18 Fab displays a second cleft between CDRH3 and CDRL1/CDRL3, which is not found in PGT121/10-1074 (in addition to the first cleft formed between CDRH3 and CDRH2, which is found in BG18 and PGT121/10-1074) (Fig. 2D) (27, 29). Last, as revealed by a ~25 Å resolution negative-stain single-particle electron microscopy (EM) structure of BG505 SOSIP.664 trimer in complex with BG18 and the CD4bs antibody 179NC75 (30), BG18 contacts the Env trimer at a different angle, which is shifted by 34° to 41° relative to PGT122 and 10-1074, respectively (Fig. 2, E and F).

BG18 bound preferentially to synthetic V3 glycopeptides containing oligomannose N-glycans at position Asn<sup>332</sup><sub>gp120</sub> but not to complex-type N-glycans attached to this position or to other potential N-linked glycosylation sites within gp120 (fig. S5). Thus, BG18 appears to be more closely related to 10-1074 than to PGT121 because 10-1074 binds almost exclusively on Asn<sup>332</sup><sub>gp120</sub> and not on other glycans (27, 28, 31). In a series of neutralization assays against a panel of HIV-1 pseudoviruses with deletions of specific N-linked glycosylation sites, we found that none of the glycans at the base of the V3 loop, with the exception of the Asn<sup>332</sup><sub>gp120</sub>, had an impact on neutralization activity (table S4). Together, these results indicate that BG18 is a new member of the Asn<sup>332</sup><sub>gp120</sub>-dependent class of bNAbs that is more potent and

structurally different from previously isolated PGT121 and 10-1074 (27, 28, 31). When compared to the available biochemical and structural data, our findings indicate that BG18 displays recognition properties that are more similar to 10-1074 than to PGT121 (27, 28, 31).

### Autologous viruses circulating between 2006 and 2015

Circulating plasma viruses were characterized by single-genome sequencing (SGS) (32) at five different time points during the years 2006 to 2015 during which viremia remained <400 copies/ml. *env* genes were about 15% divergent from the clade B consensus sequence, as would be predicted given the length of the infection of this subject (>20 years). The low level of viremia limited sequence analysis to 37 functional in-frame transcripts, in addition to which, we also found nonfunctional transcripts at every time point (1, 33, 34). The latter were either truncated or contained stop codons in the middle of the sequence (fig. S6A). Moreover, all sequences recovered from 2015, when the viral load was <400 RNA copies/ml, were nonfunctional (fig. S6A).

The 37 functional sequences formed three clusters based on their sequence. Cluster A contained one sequence from 2006 that was ~13% different from the rest of the sequences. This sequence was the closest to the clade B consensus sequence, as would be expected from the fact that this sequence was isolated from the earliest time point. The second and the biggest cluster, cluster B, contained sequences from all four time points: 1 sequence from 2006, 9 sequences from 2010, 13 sequences from 2013, and 10 sequences from 2014. The diversity within this cluster was low (~5%). The third cluster, cluster C, contained only three sequences, all from 2014 (Fig. 3A). In agreement with the new cluster of sequences that emerged in 2014, we saw an increase in viral diversity between 2013 and 2014 (Fig. 3B).

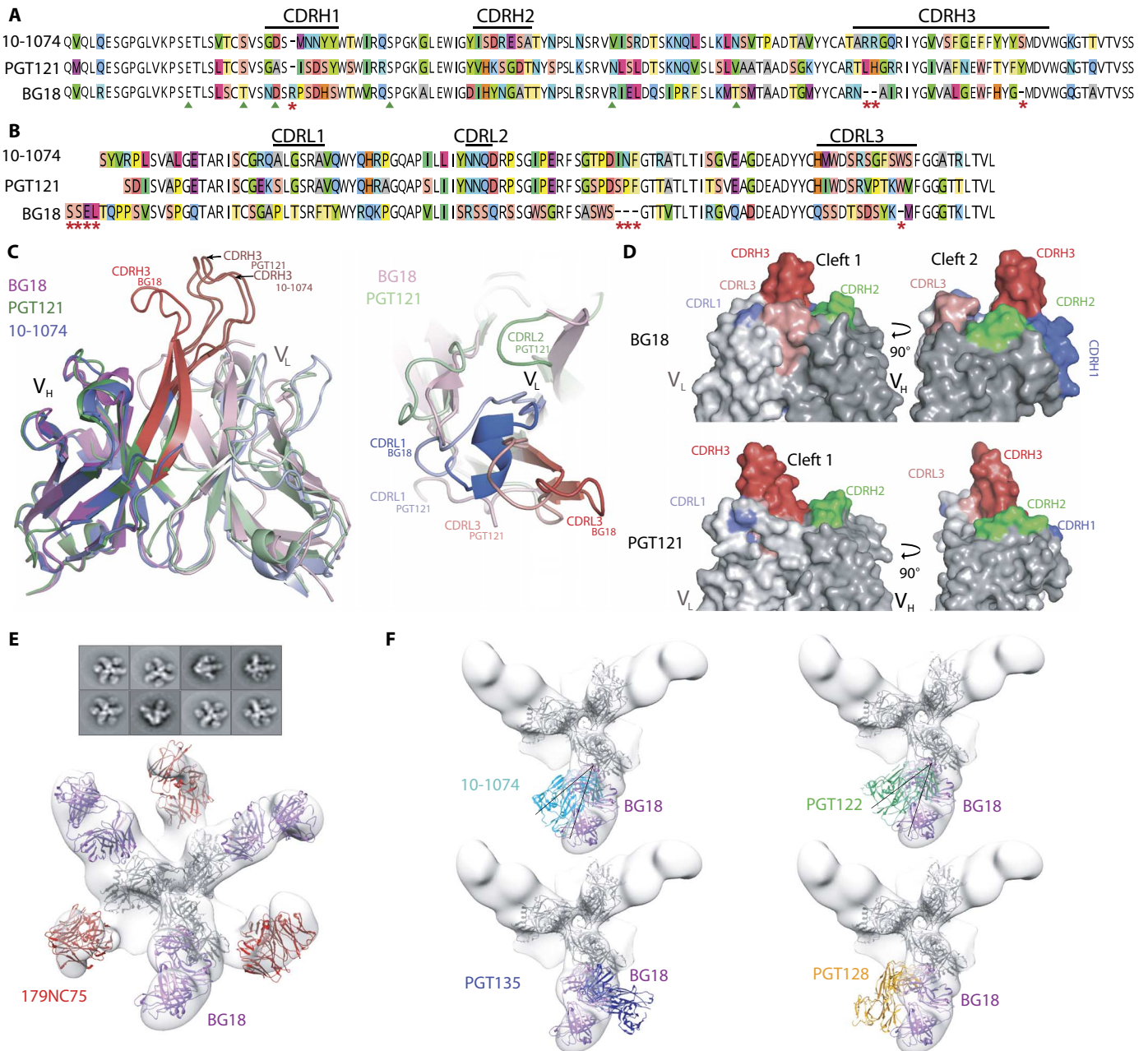
We analyzed the *env* sequences for mutations that can be associated with resistance to the three autologous bNAbs that emerged in this individual. Cluster A and B sequences did not contain any apparent mutations that were correlated with resistance to the three autologous bNAb specificities. However, all three sequences in cluster C contained mutations that deleted the N-linked glycosylation site at Asn<sup>332</sup><sub>gp120</sub> and are associated with resistance to the PGT121 class of antibodies (Fig. 3A, red arrows). In addition, they also contained a mutation associated with resistance to CD4bs antibodies (35). The sequence analysis suggests that cluster C is resistant to NC37, BG1, and BG18, whereas viruses from clusters A and B are sensitive.

### Autologous virus neutralization

To determine the sensitivity of the autologous viruses to the three autologous bNAbs, we produced pseudoviruses from the cloned *env* genes and tested them in TZM-bl assays (36). Of the 37 *env* genes, 35 were produced (2 *env* genes did not give rise to infectious particles). Of the 35 pseudoviruses produced, only 4 were resistant to all three bNAbs (that is, were not neutralized at an antibody concentration of <15  $\mu\text{g/ml}$ ). These were the three viruses from cluster C and one from cluster B isolated in 2013 (Fig. 3C, black stars, and fig. S6B). The remaining 31 pseudoviruses (88.5% of all pseudoviruses) were sensitive to at least one of the three bNAbs. In addition, the pseudoviruses from 2006, 2010, and 2014 were tested for their sensitivity to the concurrent serum IgG isolated from the same time point as the viral *env* genes (plasma IgG from 2013 was not available for this assay). We found that 19 of the 22 viruses tested were neutralized by the contemporaneous IgG (Fig. 3C and fig. S6B).

BG18- and NC37-sensitive viruses, as well as viruses sensitive to the concurrent IgG, were found at all time points analyzed, including





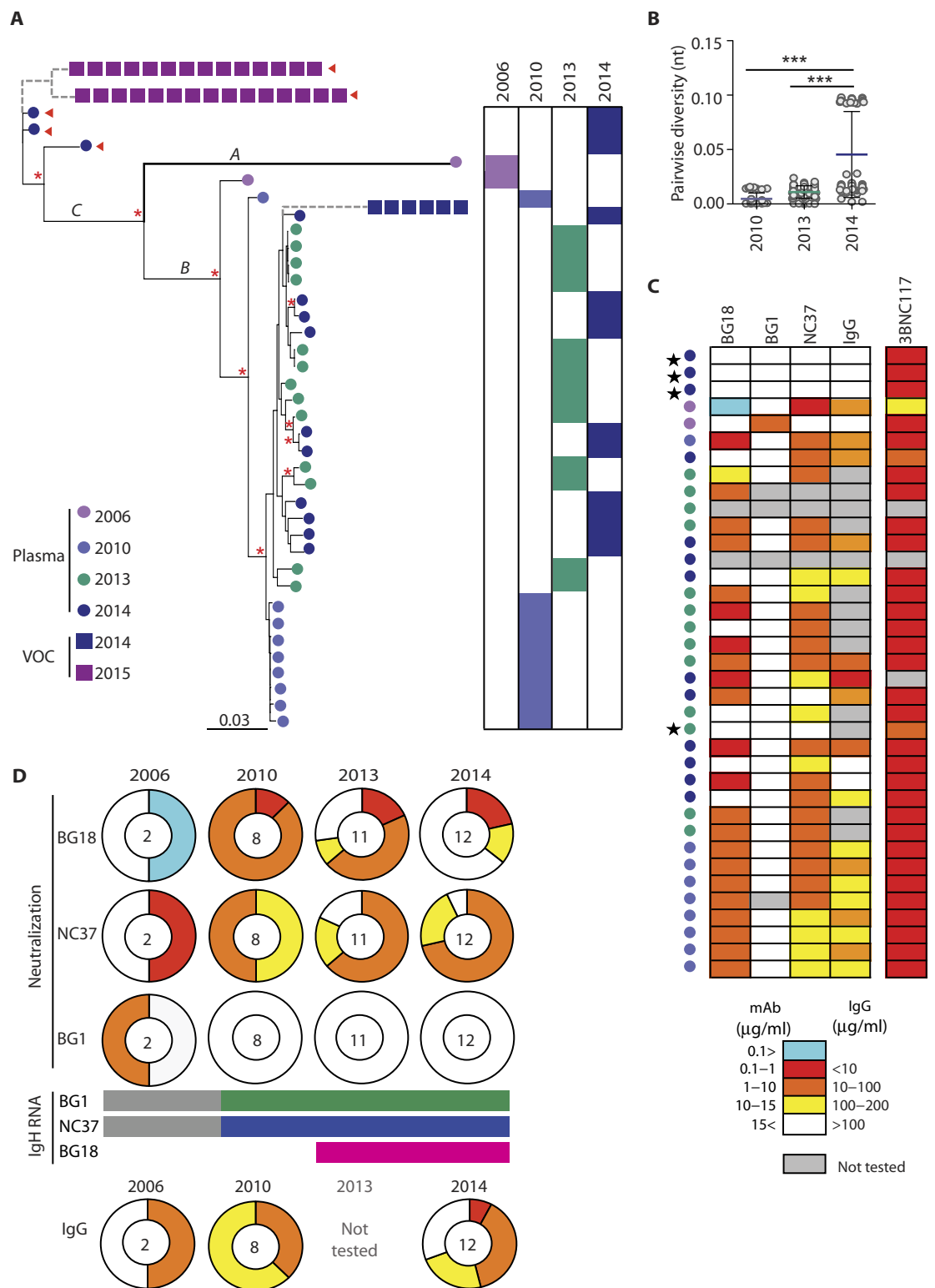
**Fig. 2. Sequence and structural analysis of BG18 bNAb.** (A) Alignment of heavy-chain amino acid sequences of 10-1074, PGT121, and BG18. The variable positions are colored according to the CPK color scheme. Red asterisks indicate gaps in alignment. Green arrows represent framework positions where all three antibodies are mutated compared to their respective germline genes. CDRH1, CDRH2, and CDRH3 are indicated. (B) Light-chain sequence alignments as in (A). (C) Left: Ribbon diagram of the  $V_H$  (dark gray) and  $V_L$  (light gray) domains of BG18 Fab as solved in 1.3 Å resolution. The CDR1, CDR2, and CDR3 loops are colored blue, green, and red, respectively. Right:  $V_L$  of BG18 (light pink) and PGT121 (light green) are shown after superimposition of  $V_H$ . The CDR1, CDR2, and CDR3 loops are colored blue, green, and red, respectively. CDRL2<sub>BG18</sub> was disordered in the crystal. 10-1074 is closely related to PGT121 and was omitted for clarity. (D) Surface representations of BG18 and PGT121; heavy chains are in dark gray, and light chains are in light gray. CDR colors as in (A). (E) Single-particle EM structure (gray transparent density) of BG505 SOSIP.664 bound to BG18 and 179NC75 Fabs. The two-dimensional (2D) class averages are given at the top panel. Coordinates for BG505 SOSIP.664 (gray ribbons), BG18 Fab (purple ribbons), and a model for 179NC75 Fab [CH103 Fab; Protein Data Bank (PDB) 4JAM] (red ribbons) were fit into the EM density as described in Materials and Methods. (F) Comparisons of angle of BG505 binding adopted by the BG18 Fab (purple) versus the Fabs of 10-1074 (41), PGT122 (PDB 5FYJ), PGT135 (PDB 4JM2), and PGT128 (PDB 5ACO). The densities for the 179NC75 Fabs were subtracted from the BG18-179NC75-BG505 map to facilitate comparisons.

the times when BG18 and NC37 were isolated (Fig. 3D). In contrast, most strains, with the exception of one virus from 2006, were resistant to BG1. We conclude that most of the autologous viruses in donor EB354 escaped from BG1 but failed to escape from BG18 and NC37.

Although we were unable to obtain viral sequences from plasma samples from 2015, we were able to grow virus from two of five  $CD4^+$  T cell outgrowth cultures from this time point (37). For control, we used a culture from 2014, a time point where we obtained sequence

**Fig. 3. Autologous plasma viruses in donor EB354.**

**(A)** Maximum-likelihood phylogenetic tree of single-genome-derived *env* gene sequences obtained from donor EB354 plasma sampled in 2006, 2010, 2013, and 2014. Red asterisk indicates clades with bootstrap support of  $\geq 90\%$ . The *env* sequences obtained from viral outgrowth cultures (VOCs) from 2014 and two cultures from 2015 were added on top of the tree as dark blue and violet squares, respectively. Red arrows indicate *env* sequences where the N-linked glycosylation site is absent. **(B)** Scatter plots depicting pairwise nucleotide (nt) sequence diversity of plasma *env* sequences from 2010, 2013, and 2014. Each dot represents the pairwise genetic difference between two sequences at a given time point. Colored bars indicate median diversity, whereas black bars indicate the interquartile range. *P* values were determined using a two-sample *U* statistic-based *Z* test. \*\*\**P* < 0.0005. **(C)** Heat maps show  $IC_{50}$  values in TZM-bl assay of BG18, BG1, and NC37 and the contemporaneous IgG against autologous EB354 pseudoviruses. Black stars mark pseudoviruses that are resistant to all three autologous bNAbs. Antibody 3BNC117 served as control. The colors of the circles on the left correspond to colors of the time points when the sequences were obtained in (A). Neutralization assays were performed in duplicate and repeated at least twice. The color code of the heat map is shown below. Gray squares indicate that the assay was not performed. **(D)** Pie charts represent the sensitivity of the autologous EB354 pseudoviruses to each one of the three bNAbs or serum IgG at the indicated time points. The number in the middle of the pies represents the number of pseudoviruses tested, and the slices are proportional to the number of pseudoviruses and are colored according to the  $IC_{50}$  sensitivity in (C). The colored bars show when antibody transcripts (IgH) were detected by PCR. Gray indicates not determined.



from circulating viruses. Two cultures from 2015 and one from 2014 grew out after a prolonged period (5 weeks versus typical of 2 weeks). The viruses emerging from the 2015 cultures resembled cluster C se-

quences in that they lacked the N-linked glycosylation site at Asn<sup>332</sup><sub>gp120</sub> (Fig. 3A, violet squares) and were resistant to all three bNAbs. The viruses emerging from the 2014 cultures were closely related to one

of the 2014 plasma viruses (2014\_C10; fig. S6). However, whereas the virus obtained from plasma showed some sensitivity to NC37 (IC<sub>50</sub>, 4.56 µg/ml), the 2014 virus that grew out in tissue culture was resistant to all three bNAbs. Despite their resistance to the bNAbs, the tissue culture outgrowth viruses did not emerge as infectious circulating viruses in the patient and were either unfit in vivo or latent.

### In vivo efficacy of BG18, NC37, and BG1

To determine whether BG18 or NC37 can exert selective pressure on HIV-1 in vivo, we infected humanized mice with HIV-1<sub>YU2</sub> and treated with the antibodies 10 to 14 days later (38). Similar to 10-1074 (38), administration of BG18 or BG8 (a less potent clonal variant) was associated with a rapid decrease (average one log<sub>10</sub>) in viral load, followed by rebound viremia [Fig. 4A (top) and figs. S7 (top) and S8A]. As expected, all rebounding viral sequences contained a mutation that altered the N-linked glycosylation site at Asn<sup>332</sup><sub>gp120</sub> (Fig. 4, B and C, top) (38).

Monotherapy with NC37 also transiently suppressed viremia, but the magnitude of the decrease in viral load was less profound than that with BG18, with an average of 0.4 log<sub>10</sub> [Fig. 4A (bottom) and fig. S7 (bottom)]. Most of the NC37-rebound viral Env sequences showed an R456K mutation that is associated with resistance to CD4bs antibodies (Fig. 4, B and C, bottom) (14, 39, 40). We conclude that BG18 and NC37 can select for HIV-1<sub>YU2</sub> antibody-resistant variants in vivo in humanized mice.

Combinations of antibodies can control HIV-1<sub>YU2</sub> infection in humanized mice (35, 38). To determine whether the combination of BG18, NC37, and BG1 can control viremia, we treated nine HIV-1<sub>YU2</sub>-infected humanized mice with a 1:1:1 combination of the three bNAbs in two independent experiments. In contrast to monotherapy with BG18 or NC37, the combination of BG18, NC37, and BG1 produced a prolonged and sustained drop in viremia (Fig. 4, D and E). Viral loads were reduced by an average of 1.48 log<sub>10</sub> shortly after administration of the three bNAbs, and six of the nine mice showed undetectable viral loads after 3 weeks (Fig. 4D). We conclude that when applied in combination, the three bNAbs that naturally developed in donor EB354 mediate potent and durable suppression of viremia in humanized mice infected with HIV-1<sub>YU2</sub>.

### DISCUSSION

Here, we describe a singular HIV-1-infected elite controller, EB354, who was followed prospectively for 9 years. During that time, EB354 donated samples for analysis at five different time points, enabling the isolation of three new bNAbs that account for serologic neutralizing activity and circulating viruses. We find that in this individual, viruses sensitive to the antibodies coexisted with the bNAbs for long periods of time.

BG18, the most potent of the three antibodies isolated from donor EB354, is directed against the Asn<sup>332</sup><sub>gp120</sub>-centered glycan patch at the base of the V3 loop. This is a heavily glycosylated region that is a frequent target for anti-HIV-1 bNAbs, which includes carbohydrates at positions Asn<sup>332</sup><sub>gp120</sub>, Asn<sup>301</sup><sub>gp120</sub>, Asn<sup>386</sup><sub>gp120</sub>, Asn<sup>392</sup><sub>gp120</sub>, Asn<sup>137</sup><sub>gp120</sub>, and Asn<sup>156</sup><sub>gp120</sub> (1, 4, 27, 31, 41, 42). A number of monoclonal bNAbs that bind to both protein and carbohydrate components at this site have been isolated, including PGT121-124, PGT128-135 (28), 10-1074 and variants (27), and the recently isolated PCDN antibodies (9). BG18 and its clonal variants resemble 10-1074 in that they rely exclusively

on Asn<sup>332</sup><sub>gp120</sub> (27, 31), but BG18 is more potent than published anti-V3 bNAbs and is the first to be isolated from a clade B donor.

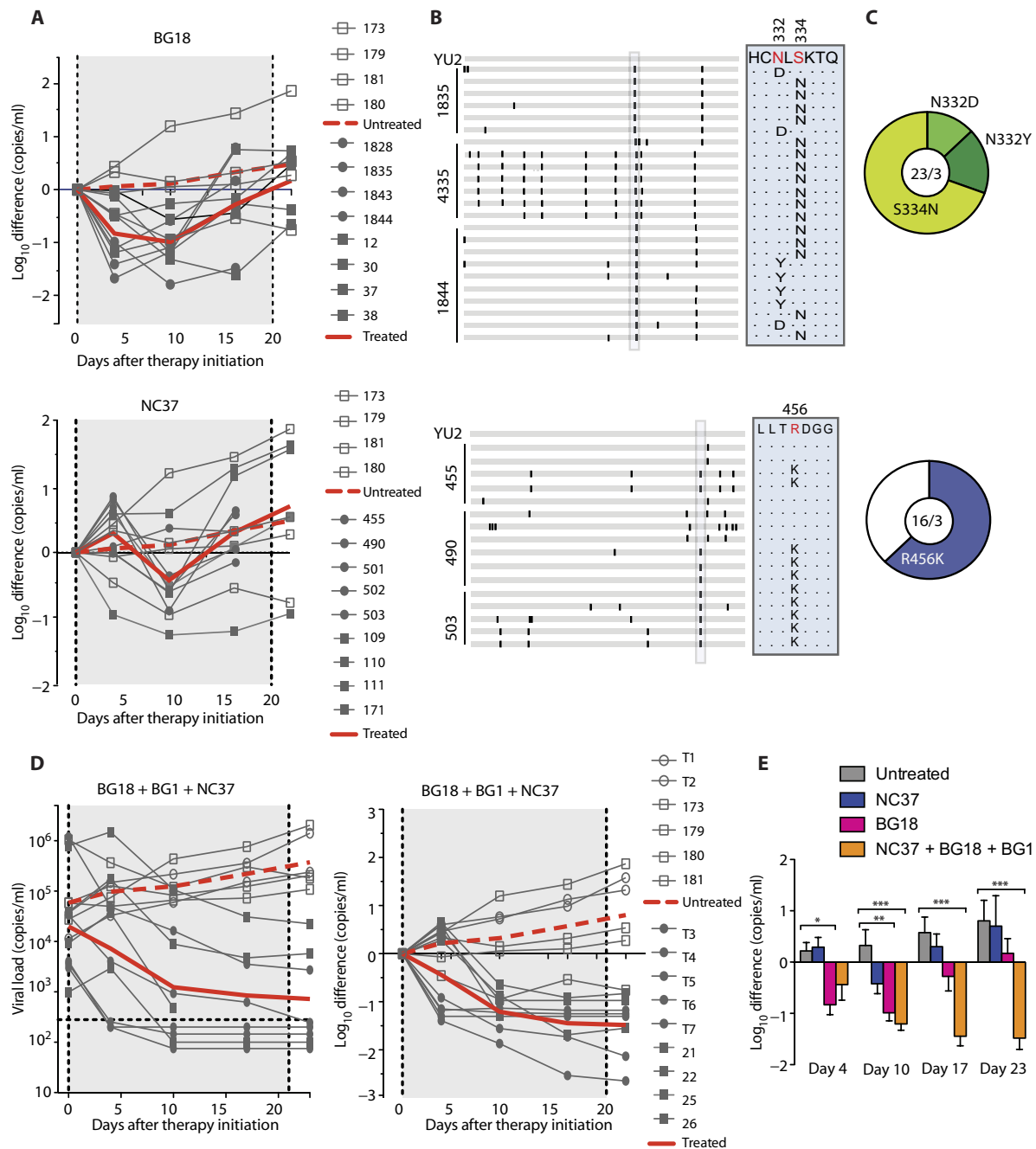
The BG18-Env EM structure, although not of sufficient resolution to identify detailed interactions, nevertheless demonstrates that BG18 approaches Env from a different angle, which is shifted by up to 40° toward the gp120 promoter relative to the approach angles of 10-1074 and PGT122 (a closely related variant of PGT121). In addition, the BG18 Fab differs from previously characterized members of this class by a distinctive orientation and a shorter length of its CDRH3. The lack of insertions or deletions in the BG18 CDRH3 suggests that BG18-like antibodies may be easier to elicit by vaccination.

The other two neutralizing specificities, in addition to BG18, are represented by BG1 and NC37. BG1 binds to the V1V2 region of Env, another frequent target of bNAbs arising during natural infection (20), and is the first antibody in this class to be isolated from a clade B-infected donor. Its potency is similar to members of the VRC26 antibody family (43) but is less potent than PG9/16 and PGDM1400 bNAbs. Like other V1V2 bNAbs isolated to date, BG1 has a long, tyrosine-rich CDRH3. The third neutralizing specificity is represented by NC37. NC37 and its clonal variants display sequence characteristics of both V<sub>H</sub>I-2- and V<sub>H</sub>I-46-derived bNAbs; however, structural analyses suggest that NC37 recognizes Env in a V<sub>H</sub>I-46-type manner (21). As a consequence, NC37 uses its light chain to the contact loop D residue Asn<sup>280</sup><sub>gp120</sub>, whereas V<sub>H</sub>I-2-derived antibodies such as NIH45-46 use their heavy chains to contact Asn<sup>280</sup><sub>gp120</sub> (40, 44, 45). Superposing the NC37 Fab-gp120 complex onto an SOSIP.664 trimer structure suggests that the long NC37 CDRH3 makes contacts with the adjacent promoter within the Env trimer, thus NC37 recognizes a quaternary trimer epitope, the core of which overlaps with the CD4bs.

Most individuals rapidly develop strain-specific antibodies shortly after infection (6, 10, 15, 46–48). This response is associated with selection for resistant viral variants that, in some cases, elicit bNAbs (5, 12, 31, 49–51). However, the individuals studied in detail differ from EB354 in that the development of bNAbs is associated with rapid selection of autologous plasma viruses, which are resistant to co-existing bNAbs (6–9, 52, 53). Donor EB354 is significant because sensitive and resistant viral strains coexist with bNAbs, and the resistant strains fail to produce high levels of viremia because the viral strains are either in some way partially effective or kept in check by CD8<sup>+</sup> T cells. Thus, the bNAb-sensitive plasma viruses were unable to escape immune pressure in this individual, resulting in bNAb:virus equilibrium, where the virus persists but is incapable of producing high levels of viremia.

EB354 is unusual in being both an elite controller and elite neutralizer. HIV-1 elite controllers are infected individuals who maintain low viral loads for many years (54–56). These individuals are less likely to transmit the virus (57), and they maintain long-term AIDS-free survival (58). HLA alleles B57\*01 and/or B27\*05 are found in 85% of HIV-1 elite controllers (19, 59), and these alleles are associated with enhanced CD8 T cell cytotoxic activity (18). Compared to viremic progressors (that is, patients with high viral loads), elite controllers are less likely to develop bNAbs (60–66). Irrespective of robust CD8<sup>+</sup> T cell responses that may have partially controlled infection, there was sufficient HIV-1 replication in EB354 to support bNAb development and affinity maturation.

Like several other individuals who develop serologic breadth and potency, the bNAbs that account for serologic neutralizing activity in donor EB354 recognize several nonoverlapping epitopes (5, 20, 21, 67–69). In some well-documented cases, the emergence of one bNAb lineage



**Fig. 4. bNAb therapy in HIV-1<sub>YU2</sub>-infected humanized mice.** (A) Graph shows changes in viral load (in  $\Delta\log_{10}$ ; y axis) in BG18- and NC37-treated HIV-1<sub>YU2</sub>-infected humanized mice plotted against days after antibody treatment (time; x axis). Mice were infected 10 to 14 days before initiation of therapy. The gray area on the graph indicates the period during which antibody was given. Each graph shows two independent experiments indicated by circles and squares. Filled symbols indicate treated mice, and open symbols indicate control mice. The dashed and solid red lines indicate the average values for control and treated mice, respectively. (B) Amino acid sequence alignment of gp120 sequences from viruses cloned on day 21 after therapy with BG18 (top) or NC37 (bottom). Each horizontal gray bar represents the sequence of a single gp120 clone aligned to HIV-1<sub>YU2</sub>. Amino acid substitutions are indicated as black ticks. The mouse ID from which the sequence was obtained is indicated on the vertical black bars and corresponds to the IDs in (A). An expanded view of the boxed areas is shown on the right in each panel. (C) Pie charts showing the recurrent mutations for BG18 (top) and NC37 (bottom) in gp120 compared to the wild-type HIV-1<sub>YU2</sub> sequence. The different slices are proportional to the number of sequences that carried mutations. The number in the center of the pie denotes the total number of sequences cloned over the number of mice from which the sequences were obtained. White slice in NC37 indicates lack of any recurrent mutations. (D) Graphs show viral load (left) and changes in viral load (right) after treatment with a combination of three antibodies, BG18 + NC37 + BG1. Each graph summarizes two independent experiments indicated by circles and squares. Filled symbols indicate treated mice and open symbols indicate control mice. The dashed and solid red lines indicate the geometric mean values (left) and average values (right) for control and treated mice, respectively. The shaded area indicates the period during which combination of bNAbs was given. (E) Changes in  $\log_{10}$  viral load (mean and SEM) for mice treated with NC37 (blue), BG18 (magenta), or the combination of NC37, BG18, and BG1 compared to controls (gray). Significant differences between groups were determined by using repeated-measures analysis of variance (ANOVA) with a Bonferroni post hoc test. \* $P < 0.05$ , \*\* $P < 0.001$ , \*\*\* $P < 0.0001$ .



facilitates the development of a second one by selecting for escape variants that expose areas on Env that support further development of additional bNAb (52). Although samples are not available to test this idea, BG1 was the earliest bNAb lineage to emerge in EB354 and may also have been a helper lineage for NC37 and/or BG18.

When combined, BG1, BG18, and NC37 durably suppressed viremia in HIV-1<sub>YU2</sub>-infected humanized mice. Although there are reports of autologous serum neutralization of circulating viruses (70), the role of monoclonal antibodies in HIV-1 control remains uncertain (51, 71–74). Our data indicate that monoclonal bNAbs and very low levels of neutralization-sensitive viruses coexist in EB354, suggesting that antibodies contribute to elite control in this individual.

HIV-1 escapes from monotherapy with bNAbs in humanized mice and humans infused with bNAbs (Fig. 4A) (35, 38, 75–78). In contrast, combination antibody therapy in humanized mice durably suppresses viremia (38, 79). In addition, infected humans treated with antibodies show enhanced humoral immunity (80) and accelerated clearance of infected cells (81), indicating that there may be immunological benefits to this form of therapy. Whether combination antibody therapy will also suppress viremia in humans remains to be determined by clinical studies. However, durable suppression of viremia in EB354 and in humanized mice treated with BG1, BG18, and NC37 suggests that combinations of bNAbs may in fact be able to contain HIV-1 infection in humans.

## MATERIALS AND METHODS

### Study design

The objective of this study was to investigate whether bNAbs can exhibit autologous neutralization in HIV-1 patients with suppressed viremia. Donor EB354 described in this study [also denoted as donor 622800 from the HIV Controller Consortium (82)] was selected on the basis of exceptional serum neutralization from a cohort of 394 long-term nonprogressors followed at the Ragon Institute, Boston. Staining with four different HIV-1 antigens and single-cell sorting of antigen-positive memory B cells allowed isolation of three new clones of bNAbs, two of which were analyzed structurally for their binding to HIV-1 Env protein. Autologous viruses were recovered from EB354 plasma, sequenced, and produced as cytomegalovirus (CMV)–Env pseudoviruses to test for sensitivity against the autologous bNAbs and the polyclonal IgG from the same time points. Last, the three new bNAbs were used to treat humanized HIV-1<sub>YU2</sub>-infected mice separately and in combination. Donor EB354 provided a written informed consent before participating in this study, and the Rockefeller University and the Massachusetts General Hospital Institutional Review Boards approved all studies involving patient enrollment, sample collection, and clinical follow-up (protocol numbers 2003P001678 and 2003P001894). For the mouse studies, this study was carried out in strict accordance with the recommendations in the *Guide for the Care and Use of Laboratory Animals* of the National Institutes of Health. The protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Rockefeller University and in accordance with established guidelines and policies at the Rockefeller University (protocol number 13618-H).

### B cell sorting and antibody isolation

Single-cell sorting of bait<sup>+</sup>CD19<sup>+</sup>IgG<sup>+</sup> B cells from donor EB354 PBMCs was conducted as previously described (20). Memory B cells

were pre-enriched with anti-CD19 magnetic beads (magnetic cell sorter) and stained using four different baits: the gp120 2CC core protein, an engineered HIV-1 gp120 displaying the CD4bs in a stabilized conformation (23); gp140<sub>YU2</sub>, an uncleaved Env trimer from HIV-1 clade B (24); a 1:1 mixture of gp140<sub>92UG37.8</sub> (clade A) + gp140<sub>CZA79012</sub> (clade C) (25); and the native-like, fully glycosylated and cleaved clade A HIV-1 Env, BG505 SOSIP.664 (26). Together, the three baits cover all known epitopes. Rescue primers were used to amplify both heavy chains (21) and Ig $\lambda$  genes (83), and regular primers were used for Ig $\kappa$  chain (84). All PCR products were sequenced and analyzed for Ig gene usage, CDR3, and the number of V<sub>H</sub>/V<sub>L</sub> somatic hypermutations [(IgBLAST ([www.ncbi.nlm.nih.gov/igblast](http://www.ncbi.nlm.nih.gov/igblast)) and IMGT ([www.imgt.org](http://www.imgt.org)))]. Purified, digested PCR products were cloned into human Igy1, Ig $\kappa$ , or Ig $\lambda$  expression vectors as previously described (84) and produced by transient transfection of IgH, Ig $\kappa$ , and Ig $\lambda$  expression plasmids into exponentially growing human embryonic kidney 293-6E cells as previously described (85).

### Neutralization studies

HIV-1 neutralization was evaluated using the luciferase-based TZM-bl cell assay (86). Briefly, env pseudoviruses were incubated with five-fold serial dilutions of single antibodies and applied to TZM-bl cells that carry a luciferase reporter gene. After 48 hours, cells were lysed, and luminescence was measured. IC<sub>50</sub> and IC<sub>80</sub> reflect single antibody concentrations that caused a reduction in relative luminescence units by 50 and 80%, respectively. Coverage curves were built using the Antibody Database computational tool (87).

### Structural studies

X-ray diffraction data were collected for crystals of BG18<sub>N26Q</sub> Fab and NC102 Fab, and an NC37 Fab–93TH057 gp120 complex at the Stanford Synchrotron Radiation Lightsource beamline 12-2 outfitted with a Pilatus 6M pixel detector (Dectris). XDS software was used to index, integrate, and scale the data (88). The structures of BG18<sub>N26Q</sub> and NC102 Fabs were solved by molecular replacement using V<sub>H</sub>V<sub>L</sub> domains from related Fabs with CDR loops removed and C<sub>H</sub>1C<sub>L</sub> as search models and refined with Phenix (43) and manual model building in Coot (89). The NC37 Fab–93TH057 gp120 complex structure was solved by molecular replacement using the NC102 V<sub>H</sub>V<sub>L</sub> and C<sub>H</sub>1C<sub>L</sub> domains and a truncated gp120 core (from PDB 3U7Y) as search models. Data collection and refinement statistics are presented in table S4.

The structure of a BG505 SOSIP.664–BG18–179NC75 complex was solved by cryoelectron tomography/subtomogram (averaging to ~40 Å resolution) and used as a reference structure to solve a single-particle EM structure from negatively stained samples. A total of 25,639 BG505 SOSIP.664–BG18–179NC75 complex particles were picked and contrast transfer function–corrected using EMAN2.1 (90). A total of 9827 particles corresponding to good class averages were selected, and the particles were further sorted using 3D classification in RELION (91), after which, 7925 particles were selected for refinement. The resolution of the final single-particle reconstruction was ~25 Å, calculated using RELION and a gold-standard Fourier shell coefficient with a 0.143 cutoff (91). Coordinates from crystal structures were fit into the single-particle EM structure using UCSF Chimera. We first fit a BG505 SOSIP.664 structure (PDB 4TVP) into the density and then fit coordinates for BG18 and CH103 Fabs (PDB 4JAM; as a model for 179NC75 Fab) into corresponding densities individually.



**Autologous virus**

For SGS, HIV-1 RNA was extracted from patient plasma using the Qiagen MinElute Virus Spin Kit according to the manufacturer's instructions. Extracted RNA was subjected to Env-specific complementary DNA synthesis using the SuperScript III Reverse Transcriptase and HIV-1-specific primer envB3out (see the Supplementary Materials for complete primers sequences). First-round PCR was performed in a 20- $\mu$ l volume containing 1 $\times$  High-Fidelity buffer, 2 mM MgSO<sub>4</sub>, 0.2 mM deoxynucleotide triphosphates, and 0.5 U of High-Fidelity Platinum Taq using 0.2  $\mu$ M each of primers envB5out and envB3out. Second-round PCR was performed using 1  $\mu$ l of PCR-1 and 0.2  $\mu$ M primers of envB5in and envB3in. PCR conditions were the same as PCR-1 except for 45 cycles and an increased annealing temperature of 58°C. PCR-2 products were checked using 1% 96-well E-Gel (Invitrogen). Bands from PCRs with amplification efficiencies lower than 30% were subjected to library preparation and sequenced using the Illumina Nextera DNA Sample Preparation Kit. CMV-Env expression cassettes were generated according to an established protocol (36). CMV-Env (500 ng) was cotransfected with pSG3 $\Delta$ env in six-well plates into 293T cells, and the supernatant was harvested after 48 hours. All plasmids were sequence-validated before expression. Supernatants were subjected to neutralization testing by TZM-bl assay as described above.

**In vivo mouse model**

All experiments were performed under protocols approved by the university's IACUC. Humanized nonobese diabetic *Rag1*<sup>-/-</sup>*Il2rg*<sup>null</sup> (NOD.Cg-*Rag1*<sup>tm1Mom</sup> *Il2rg*<sup>tm1Wjl/SzJ</sup>) mice (the Jackson Laboratory) were subcutaneously treated with 1 mg of each antibody twice a week for a period of 3 weeks (38), receiving a total of six antibody injections. Control humanized mice were reconstituted with human cells from the same donor and infected with HIV-1<sub>YU2</sub> but not treated with antibodies. Plasma viral loads were measured weekly. The gp120 sequences from mice with rebounding virus were obtained as previously described (38).

**Statistical analyses**

Statistical differences between IgG neutralizing activity against HIV-1<sub>YU2</sub> and various mutants were analyzed by Mann-Whitney test. Significant changes in viral load between mice treated with either BG18, NC37, or the combination of BG18, NC37, and BG1 or untreated controls were determined by using repeated-measures ANOVA with a Bonferroni post hoc test considering \**P* < 0.05, \*\**P* < 0.01, and \*\*\**P* < 0.001.

**SUPPLEMENTARY MATERIALS**

www.sciencetranslationalmedicine.org/cgi/content/full/9/373/eaal2144/DC1

**Methods**

Fig. S1. Isolation of neutralizing antibody clones from donor EB354.

Fig. S2. Competitive ELISA.

Fig. S3. NC37 Fab-gp120 complex structure.

Fig. S4. Sequence comparison between BG18, PGT121, and 10-1074.

Fig. S5. BG18 antibody binding to synthetic HIV-1 V3 glycopeptides.

Fig. S6. env SGS of plasma virus from donor EB354.

Fig. S7. Viral loads in HIV-1<sub>YU2</sub>-infected and BG18- and NC37-treated humanized mice.

Fig. S8. BG8 therapy in HIV-1<sub>YU2</sub>-infected humanized mice.

Table S1. Clinical information, donor EB354 (provided in Excel).

Table S2. IC<sub>50</sub> and IC<sub>80</sub> values in TZM-bl assay for antibodies NC37, BG1, BG18, BG8, and 10-1074 and PGT121 against a 118-virus panel (provided in Excel).

Table S3. IC<sub>50</sub> and IC<sub>80</sub> values in TZM-bl assay of the 1:1:1 combination of NC37, BG1, and BG18 against a 118-virus panel (provided in Excel).

Table S4. IC<sub>50</sub> and IC<sub>80</sub> values in TZM-bl assay of antibodies BG8, BG18, PGT121, and 12A12 against selected HIV-1 V3 envelope mutants (provided in Excel).

Table S5. Crystallization statistics (provided in Excel).

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**Acknowledgments:** We thank the donor for his participation in this study. We thank Z. Jankovic for the Rockefeller University laboratory support; T. Eisenreich for help with mouse colony management; K. Velinson and N. Thomas for single-cell fluorescence-activated cell sorting; T. Schoofs for help with mice experiments and statistical analyses; G. Jensen and A. McDowall for use of EMs at Caltech; I. Nangiana, J. Vielmetter, and the Caltech Protein



Expression Center for expression of proteins used for structural studies; J. P. Moore and A. Cupo for providing and developing the BG505.664 bait; and all the great members of the Nussenzweig and Bjorkman laboratories for helpful discussion and advice. **Funding:** This work was supported by the Robertson Foundation, the Rockefeller University, the Bill and Melinda Gates Foundation grant OPP1033115, the Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery Scripps grant UM1 AI 100663, the NIH HIV Vaccine Research and Design grant 1 P01 AI100148 (to M.C.N. and P.J.B.), the NIH grant 2 P50 GM082545-06 (to P.J.B.), the Molecular Observatory and EM funding at Caltech supported by the Gordon and Betty Moore Foundation, the Melinda and Bill Gates Foundation Collaboration for AIDS Vaccine Discovery grant OPP1032144 (to M.S.S.), and the California HIV/AIDS Research Program (CHRP grant F12-CT-214 to S.A.S.). **Author contributions:** N.T.F. planned and performed experiments, analyzed the data, and wrote the manuscript. H.W. solved the EM structure. L.S. and S.A.S. solved and analyzed crystal structures and contributed to the manuscript preparation. L.N. propagated viral cultures and helped with mouse experiments. J.A.H. propagated viral cultures, performed SGS, and contributed to the manuscript preparation. A.H.-S and Y.B.-O. helped with humanized mice experiments. J.G. and A.G. produced antibodies. J.C.C.L. performed SGS and phylogenetic and diversity analyses and helped in analyzing the data. A.P.-T. and I.T. provided the human samples and coordinated with the donor. H.B.G. refined structural structures. M.J.v.G. and R.W.S. produced and provided reagents and critically read the manuscript preparation. A.P.W. analyzed antibody sequence data. H.C. and L.-X.W. performed the glycopeptide synthesis and binding

experiments. D.S. and M.S.S. performed and analyzed the neutralization assays. D.R.B. critically read and contributed to the manuscript preparation. B.D.W. provided human samples and contributed to the manuscript preparation. A.P.W. performed sequence alignment and analyses. P.J.B. planned and analyzed structural experiments and helped write the manuscript. M.C.N. planned and supervised the experiments, analyzed data, and wrote the manuscript. **Competing interests:** M.C.N. and B.D.W. are Howard Hughes Medical Investigators. The other authors declare that they have no competing interests.

Submitted 22 July 2016

Resubmitted 14 October 2016

Accepted 8 December 2016

Published 18 January 2017

10.1126/scitranslmed.aal2144

**Citation:** N. T. Freund, H. Wang, L. Scharf, L. Nogueira, J. A. Horwitz, Y. Bar-On, J. Golijanin, S. A. Sievers, D. Sok, H. Cai, J. C. Cesar Lorenzi, A. Halper-Stromberg, I. Toth, A. Piechocka-Trocha, H. B. Gristick, M. J. van Gils, R. W. Sanders, L.-X. Wang, M. S. Seaman, D. R. Burton, A. Gazumyan, B. D. Walker, A. P. West Jr., P. J. Bjorkman, M. C. Nussenzweig, Coexistence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic controller. *Sci. Transl. Med.* **9**, eaal2144 (2017).



## Coexistence of potent HIV-1 broadly neutralizing antibodies and antibody-sensitive viruses in a viremic controller

Natalia T. Freund, Haoqing Wang, Louise Scharf, Lilian Nogueira, Joshua A. Horwitz, Yotam Bar-On, Jovana Golijanin, Stuart A. Sievers, Devin Sok, Hui Cai, Julio C. Cesar Lorenzi, Ariel Halper-Stromberg, Ildiko Toth, Alicja Piechocka-Trocha, Harry B. Gristick, Marit J. van Gils, Rogier W. Sanders, Lai-Xi Wang, Michael S. Seaman, Dennis R. Burton, Anna Gazumyan, Bruce D. Walker, Anthony P. West, Jr, Pamela J. Bjorkman and Michel C. Nussenzweig (January 18, 2017)  
*Science Translational Medicine* **9** (373), . [doi: 10.1126/scitranslmed.aal2144]

### Editor's Summary

#### Antibodies can hold HIV-1 at an impasse

Neutralizing antibodies put selective pressure on pathogens to mutate and escape from immune detection, which is one of the reasons why HIV-1 infection is difficult to contain. In this issue, Freund *et al.* studied samples spanning almost a decade from an individual who naturally controls HIV-1 infection without progressing to AIDS. They discovered three potent antibodies coexisting with viral strains that were sensitive to antibody neutralization, indicating that these antibodies may be contributing to viral control. These antibodies were also able to prevent HIV-1 viremia in humanized mice, demonstrating that the antibodies may be beneficial as passive immunotherapy for infected individuals.

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