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Long-Term Control of Viral Replication in a Group O, Human Immunodeficiency Virus Type 1-Infected Individual

Robert W. Buckheit III,[1,*] Stephen B. Sexauer,[1] Ahmad R. Sedaghat,[2] Claus O. Wilke,[3,4] Oliver Laeyendecker,[1,5] Christie R. Basseth,[1] and Joel N. Blankson[1]

EDITOR: HIV-1 is classically classified into three main groups: M (major), N (non-M, non-O), and O (outlier),[1] with Group P being identified most recently.[2] Evolutionary studies suggest each group represents a distinct cross species transmission of SIV_{cpz} or SIV_{gor} into the human population.[2,3] HIV-1, Group O has mostly remained endemic to Cameroon and inaccurate diagnosis of Group O infection is a major barrier to treatment in this country.[4] A unique subset of individuals, termed long-term nonprogressors (LTNPs), is able to maintain stable $CD4^+$ T cell counts for greater than 5 years in the absence of antiretroviral therapy. Here we report a patient infected with a Group O HIV-1 isolate who has maintained long-term control of HIV replication in the absence of antiretroviral treatment (ART).

The patient is a 38-year-old treatment-naive female originally from Cameroon. She was diagnosed with HIV-1 infection in 1998 in Cameroon, and first presented to the United States in 2004 with an initial CD4 count of 576 and a viral load of <50 copies/ml as measured by the Roche AMPLICOR HIV-1 MONITOR 1.5 ultrasensitive assay. She maintained stable $CD4^+$ T cell counts and viral loads of <50 copies/ml in the absence of ART (Fig. 1A) over the next 6 years. The rate of $CD4^+$ T cell decline was calculated as described previously.[5] We found that there was no significant decline in $CD4^+$ T cells between 2005 and 2010 ($p=0.0615$). HLA typing revealed that she was HLA-A*02/66 and HLA-B*42/53 positive.

Virus was cultured from the patient's latent reservoir as previously described[6] in 2010 and designated JHGO1. Phylogenetic analysis was performed on full length *env* sequences of the patient's virus compared to Group O, N, and M isolates. Classical, maximum likelihood, and Bayesian phylogenetic analysis was performed. The patient's virus was most closely related to HIV-1, Group O (Fig. 1B). Group O nested-PCR primers were developed utilizing full genome Group O sequences from the Los Alamos HIV Sequence database and full genome sequencing was performed (GenBank accession number JN571034). No gross sequence defects were seen compared to other Group O viral sequences. Evolutionary differences in Group O reverse transcriptase (RT) have resulted in resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) in many treatment-naive patients.[7] The patient's virus had mutations A98G, V179E, and Y181C in RT (Fig. 1C), all of which have been reported to confer resistance to NNRTIs.[7] The virus isolated from the patient's latent reservoir was found to be as replication-competent as a Group O HIV-1 laboratory strain (HIV-1 BCF1[8]) in a viral fitness assay where activated $CD4^+$ T cells from seronegative donors were infected with 200 ng/ml p24 of either the patient's isolate or the laboratory strain as previously described[6] and HIV-1 RNA in culture supernatant was quantified on day 5 postinfection with the Abbott m2000 RealTime HIV Assay (Fig. 1D).[9]

The patient's plasma viral load was subsequently determined to be 2,682 RNA copies/ml by the Abbott m2000 RealTime HIV Assay. The Roche AMPLICOR HIV-1 MONITOR test remained <50 copies/ml consistent with studies showing that the latter test does not routinely detect Group O HIV-1 isolates.[9]

Taken together, although this patient was initially misclassified as an elite controller, her stable $CD4^+$ T cell counts and low viral load indicate that she is a long-term nonprogressor (LTNP). LTNPs have previously been identified in Group M infection, but to our knowledge, long-term nonprogression in patients infected with a Group O virus has not been previously reported. Infection with a defective virus accounts for some cases of long-term nonprogression,[10] but multiple studies have also shown that replication-competent virus can be isolated from some LTNPs and elite controllers.[11] It is clear that host factors, such as protective HLA types and HIV-specific $CD8^+$ T cells, play a large role in the control of HIV-1 infection.[12] This patient possessed no previously reported protective HLA alleles, but a substantial proportion of LTNPs and elite controllers (EC) do not have these alleles.[13] Our fitness assay results

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.
[2]Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.
[3]Section of Integrative Biology, Center for Computational Biology and Bioinformatics, Austin, Texas.
[4]Institute for Cell and Molecular Biology, University of Texas at Austin, Austin, Texas.
[5]Division of Intramural Research, NIAID, NIH, Baltimore, Maryland.
*Current affiliation: Virus Cell Interaction Section, HIV Drug Resistance Program, National Cancer Institute, Frederick, Maryland.

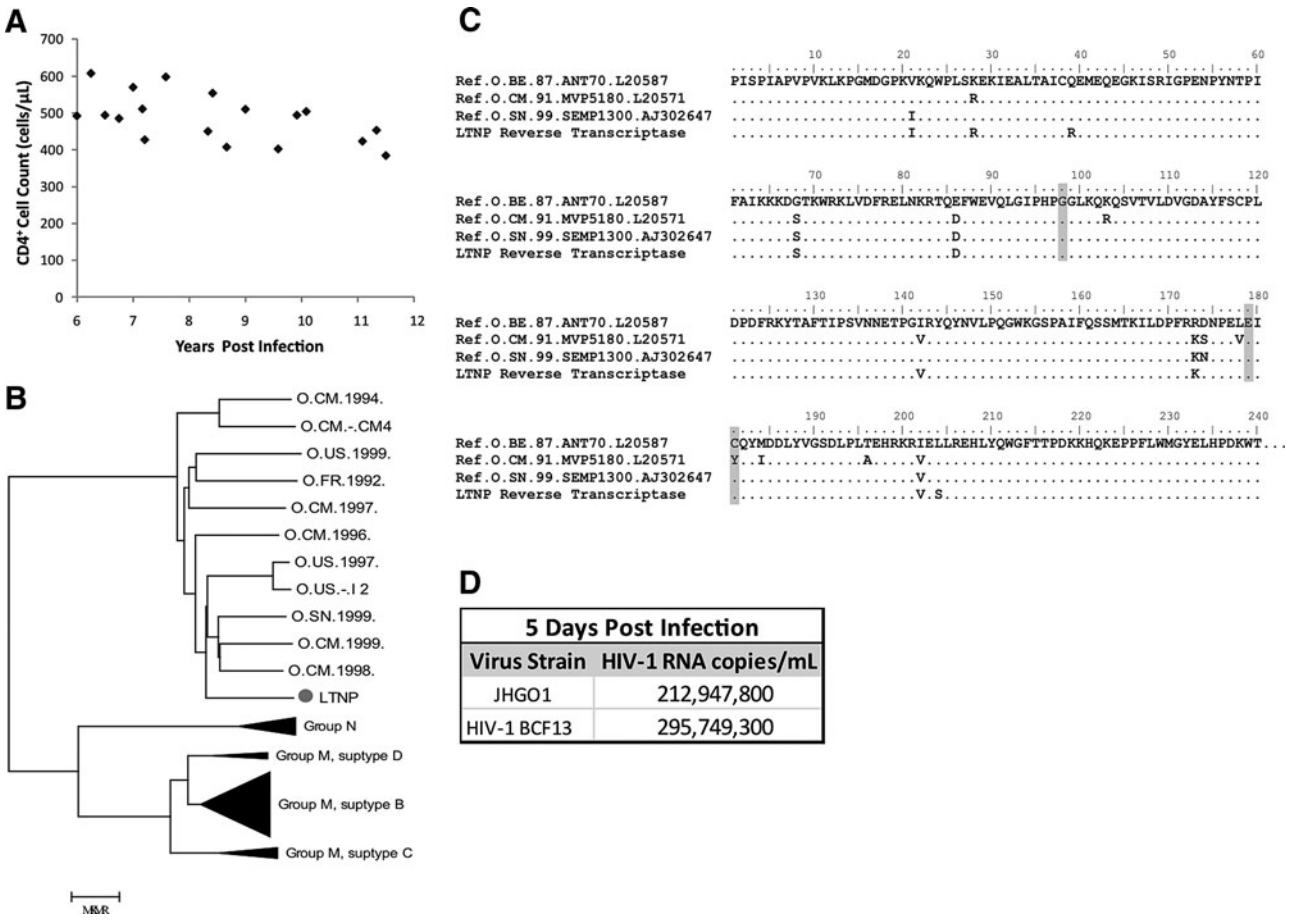

FIG. 1. **(A)** Patient's CD4 count over time. **(B)** Phylogenetic analysis demonstrating that the *env* sequence from the patient's isolate (gray dot) clusters with the *env* sequence from Group O isolates. **(C)** Reverse transcriptase sequence from the patient and two other Group O isolates showing the presence of nonnucleoside reverse transcriptase inhibitor mutations (gray). **(D)** HIV RNA copies/ml in culture supernatant at day 5 postinfection with the patient's isolate (JHG01) or a laboratory isolate.

suggest that this patient is not infected with a defective virus. While we were not able to study HIV-specific $CD8^+$ T cell function in this patient, it appears that host factors were responsible for control of viral replication. This case suggests that some Group O-infected individuals can partially control fully pathogenic virus.

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Address correspondence to:
Joel N. Blankson
Department of Medicine
Johns Hopkins University School of Medicine
733 North Broadway, BRB 880
Baltimore, Maryland 21205

E-mail: jblanks@jhmi.edu