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MAJOR ARTICLE

Dynamic Visual Display of Treatment Response in HIV-Infected Adults

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Background. Using a dynamic visual display, we examine the changes in human immunodeficiency virus type 1 (HIV-1) plasma viral load and CD4 cell count for 5 years after antiretroviral therapy initiation in a large cohort of patients with HIV.

Methods. Patients at a Centers for AIDS Research Network of Integrated Clinical Systems site who initiated combination antiretroviral therapy between 1 January 2000 and 31 December 2012 were followed for 5 years for HIV-1 plasma viral load, CD4 cell count, and mortality. The joint distribution of CD4 cell count and viral load over time was depicted in an animated display using a bivariate kernel smoother.

Results. Within days of therapy initiation, many patients had a suppressed viral load and their median CD4 cell count had increased. However, the median CD4 cell count remained below normal levels throughout follow-up period and the proportion of patients with high viral load occasionally increased, even years after therapy initiation.

Conclusions. The dramatic changes in viral load and CD4 cell count after therapy initiation highlight the overwhelming effectiveness of antiretroviral therapy in the modern era. However, this work also emphasizes the need for pharmaceutical or behavioral interventions to prevent virologic failure and to stimulate complete recovery of normal CD4 cell count.

Keywords. HIV/AIDS; antiretroviral therapy.

A primary goal of clinical care for patients with human immunodeficiency virus (HIV) infection is to improve disease-free survival. To accomplish this goal, patients with HIV have historically initiated combination antiretroviral therapy when their CD4 cell count drops below a predefined threshold or, more recently, shortly after entering routine HIV care. Ideally, therapy initiation will result in a decrease in plasma HIV-1 RNA (or viral load) to undetectable levels and a subsequent increase in CD4 cell count. However, patients have heterogeneous immunological responses to therapy. Here, we use a dynamic visual display to examine the changes in viral load and CD4 cell count for 5 years after therapy initiation among 12 968 patients in care at 1 of 8 sites in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) in the United States. These visual displays of immune system responses to antiretroviral therapy can be used to explore differences in immune system response by patient characteristics or behaviors. This information can be used, in turn, to design clinical or public health interventions in order to improve treatment response for patients with HIV.

METHODS

CNICS is a partnership among 8 Centers for AIDS Research in the United States to collect standardized clinical data for population-based HIV research [1]. The CNICS cohort includes more than 29 000 adults living with HIV who are engaged in clinical care at 1 of the 8 sites (Case Western Reserve University; Fenway

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Community Health Center of Harvard University; Johns Hopkins University; University of Alabama at Birmingham; University of California, San Diego; University of California, San Francisco; University of North Carolina; and University of Washington). All patients who attend 2 primary HIV medical care visits at study sites are eligible to be enrolled in CNICS and followed longitudinally while they remain in care at study sites [1]. Institutional review boards at each site approved study protocols.

Here, we included patients who initiated combination antiretroviral therapy (defined as simultaneous initiation of 3 or more antiretroviral drugs) between 1 January 2000 and 31 December 2012. We included patients with both CD4 cell count and HIV-1 viral load measurements between 100 days before and 15 days after therapy initiation. Patients were followed from 100 days prior to therapy initiation until death or administrative censoring 1800 days (about 5 years) after therapy initiation. Deaths among patients in CNICS are verified using the US Social Security death index.

To examine patients' responses to therapy, we followed patients for mortality, CD4 cell count, and viral load. Cumulative all-cause mortality was estimated using the complement of the Kaplan–Meier product limit estimator of the survivor function [2]. To account for differences in the frequency of CD4 cell count and viral load measurements, we weighted each visit by the inverse probability of being observed during a given day [3] (details provided in Supplementary Appendix A). We examined the joint distribution of CD4 cell count and viral load over time using a bivariate kernel smoother [4, 5] (details provided in Supplementary Appendix B). Intent to continue therapy following treatment initiation was implied, and analyses do not account for gaps in treatment and/or treatment discontinuation. In the text, we summarize the changes in distribution of CD4 cell count and proportion of patients with a suppressed viral load over time. For the purposes of this article, we consider a patient to have a suppressed viral load if his/her viral load is <500 copies/mL. While the limit of detection for HIV-1 RNA was 50 copies/mL at most sites during the study period, some sites had higher limits of detection for some of this time. Therefore, to ensure that no patient was misclassified as having an unsuppressed viral load due to a higher limit of detection, we set the threshold value higher than the all limits of detection in place during the study.

Python code to create the dynamic graphs of the joint density of CD4 cell count and viral load is provided in Supplementary Appendix C.

Table 1. Demographics and Clinical Characteristics at Study Entry of 12 968 Patients Who Were Linked to Care at a Centers for AIDS Research Network of Integrated Clinical Systems Site and Initiated Combination Antiretroviral Therapy Between 1 January 1998 and 31 December 2012 at 8 US Clinical Sites

	All Patients at Therapy Initiation (n = 12 968)	
Characteristic	n	%
Male	10 625	82
Black	4648	37
Hispanic	1862	14
Injection drug user	1808	14
Men who have sex with men	7823	61
AIDS	3109	24
Year at study entry		
1998–2002	2348	18
2003–2007	4606	36
2008–2013	6013	46

RESULTS

Table 1 presents the characteristics of the study sample. Among the 12 968 eligible patients, 82% were male, 37% were black, 14% were injection drug users, and 61% were men who have sex with men. During the follow-up period, patients attended 188 637 visits at which CD4 cell count or viral load measurements were recorded. The static Figure 1 illustrates the joint distribution of CD4 cell count and viral load at 4 time points relative to therapy initiation: 30 days prior to therapy initiation and 30 days, 90 days, and 3 years after therapy initiation. The surface represents the density of the joint distribution of CD4 cell count and viral load, while the univariate distributions of CD4 cell count and viral load can be seen individually on the rear walls of the plot. Changes in the joint distribution of CD4 cell count and viral load over time can be seen in the animated version of Figure 1 provided online (Supplemental video).

One month prior to therapy initiation, most patients (89%) had unsuppressed viral load (>500 copies/mL). The median viral load was 60 270 copies/mL (interquartile range [IQR], 14 022, 211 413), and the median CD4 cell count was 211 cells/mm^3 (IQR, 47, 379; panel A). Note that prior to combination antiretroviral therapy initiation, 14% of patients received at least 1 prescription for monotherapy or dual therapy during their time in HIV care. Within 30 days after therapy initiation, viral loads decreased dramatically and CD4 cell counts increased (panel B). At 90 days after therapy initiation, most patients had suppressed viral loads of ≤500 copies/mL (79%; panel C) and the median CD4 cell count was 344 (IQR, 184, 518). At 3 years after therapy initiation, most patients continued to have a suppressed viral load (79%) and the distribution of CD4 cell counts slowly continued to shift higher (median, 472; IQR, 280, 663). However, even after therapy initiation, some patients continued to have low CD4 cell count and high viral load. Values for these patients can be seen on the far right of the figures and animation.

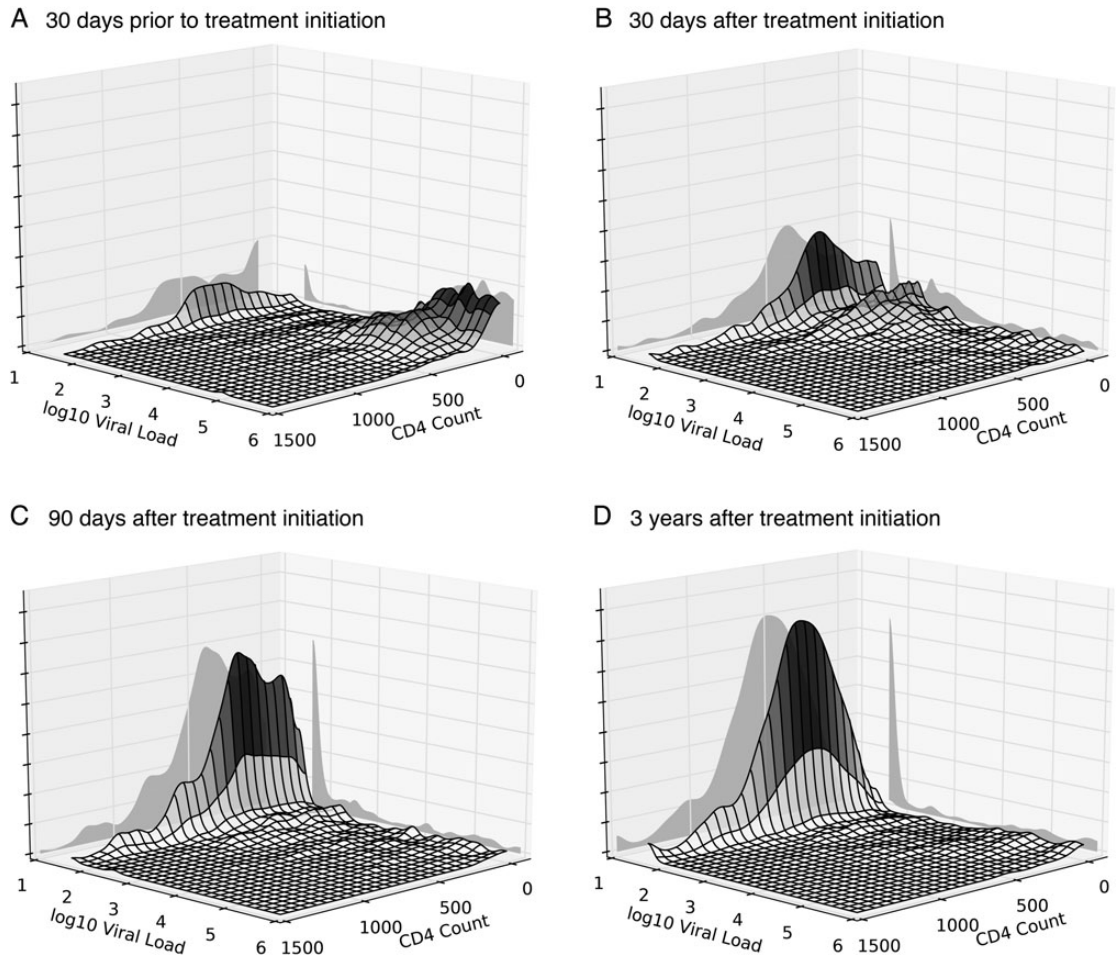

Figure 1. Joint distribution of CD4 cell count and viral load at 30 days prior to therapy initiation (panel *A*) and 30 days (panel *B*), 90 days (panel *C*), and 3 years (panel *D*) after therapy initiation for 12 968 patients with human immunodeficiency virus infection in care at 1 of 8 Centers for AIDS Research Network of Integrated Clinical Systems sites across the United States from 2000 to 2012. For an animated version of this figure, please see the supplementary video.

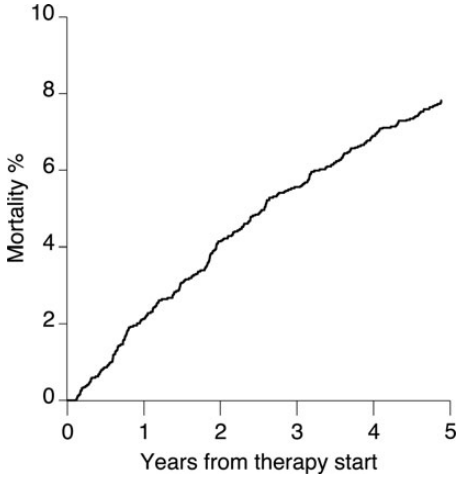

Figure 2. Cumulative incidence of mortality for 12 968 patients who entered care between 1 January 1998 and 31 December 2012 at 8 US clinical sites and were followed for death up to 5 years.

Figure 2 presents the cumulative mortality estimates over the 5-year study period. During follow-up, 994 patients died, and the estimated cumulative mortality was 7.8% at the end of the 5-year study period (284 deaths had occurred at the end of 1 year; 1-year cumulative mortality was 2.1%). The deaths occurring at each time point are illustrated in the online animation by red circles at the value of the patient's last recorded CD4 cell count and viral load. Figure 3 presents the joint distribution of the last observed CD4 cell count and viral load for patients who died during the study period within 1 year of their last laboratory measurements (906/994 deaths). The 88 patients who died more than 1 year after their last recorded laboratory measurements were excluded from Figure 3. Among patients who died with laboratory measurements within 1 year of death, the median CD4 cell count at the last clinic visit was 125 cells/mm^3 (IQR, 28, 310) and 49% had an unsuppressed viral load >500 copies/mL.

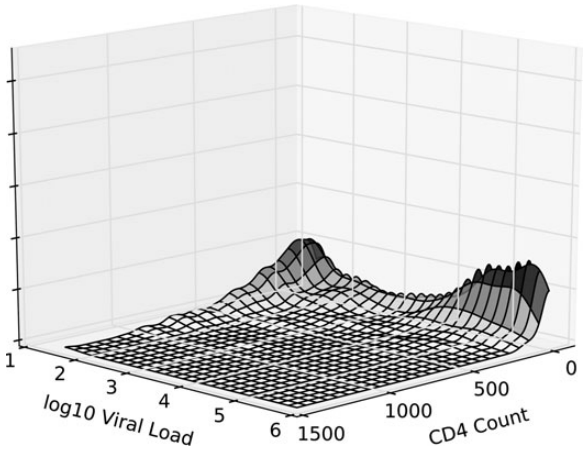

Figure 3. Joint distribution of the last observed CD4 cell count and viral load for 906 patients with human immunodeficiency virus infection who died within 5 years of therapy initiation while in care at 1 of 8 Centers for AIDS Research Network of Integrated Clinical Systems sites across the United States from 2000 to 2012.

DISCUSSION

Within 1 month of treatment, most patients experienced a dramatic drop in viral load. CD4 cell count recovered more slowly. Despite a gradual increase in CD4 cell count following therapy initiation, most patients did not recover a normal level of CD4 cell count (>800 cells/mm^3) during the 5-year study period as previously observed [6, 7].

In the animation and figures, which are largely model-free representations of the data, we can see that patients had heterogeneous responses to therapy [8]. Therapy was clearly successful for some patients who initiated therapy when their HIV-1 RNA viral load was >50 000 copies/mL and their CD4 cell count was low and rapidly suppressed their viral load to <500 copies/mL and recovered CD4 cell count. On the other hand, therapy was not successful for a number of patients who had unsuppressed viral load (>500 copies/mL) and low CD4 cell count years after therapy initiation. In Figure 3, we could see that most patients who died following therapy initiation had low CD4 cell count at the measurement taken closest to their death, and many of the patients who died also had unsuppressed viral load.

The earthquake-like changes in the topology of HIV-1 RNA viral load around therapy initiation highlight the overwhelming effectiveness of antiretroviral therapy in the modern era. However, the dynamic visual display of changes in CD4 cell count and HIV-1 viral load over time also emphasizes areas for improvement. We must continue to develop pharmaceutical or behavioral interventions to prevent virologic failure for patients receiving antiretroviral therapy and to stimulate complete recovery of normal CD4 cell count. Based on current knowledge, the failure of antiretroviral therapy is less likely to be due to multiclass resistance emergence [9] and more likely to be due to difficulty with adherence to medications, medication access, and consistent adherence to care [10, 11]. The dynamic graphical displays depicted here offer a new tool for future work to investigate disparities in outcomes after treatment with antiretroviral therapy and to explore how biomedical or behavioral interventions might affect the immune response to therapy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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