

Research Team

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Main Findings

- While most patients with HIV do appear to be receiving care in accordance with federal guidelines for use of highly active antiretroviral therapy (HAART), a substantial proportion appear not to be receiving treatment in accordance with the guidelines.
- Treatment based on the guidelines did not vary significantly by demographic characteristics.
- Younger patients were more likely than older ones to be failing their HAART regimen based on viral load at study entry.

Background

The widespread use of HAART for the treatment of HIV has led to a dramatic decline in the incidence of death and opportunistic infections and malignancies among people with HIV. After the initial success of HAART regimens, guidelines were developed recommending that all people with HIV infection be treated early (i.e., as soon as they had 500 or fewer CD4+ cells) and aggressively in order to drive their viral loads to undetectable levels.

However, side effects associated with these medications quickly emerged, including nausea, diarrhea, neuropathy, high cholesterol levels, and changes in body shape. In addition, some patients developed resistance to their medications, causing their viral loads to increase. Despite rising viral load levels, many of these people continued to do well immunologically and clinically. That is, their CD4+ cell counts did not drop and they did not get any new opportunistic infections or malignancies.

In response to these developments, many providers and patients began to question the “hit early, hit hard” treatment strategy of the clinical guidelines. They began to delay treatment, use regimens that did not include protease inhibitors, or continue treatment on a regimen despite increases in viral load.

In an effort to understand how providers and patients were using HAART, whether they were following the clinical guidelines, and to learn more about the virologic, immunologic, and clinical outcomes associated with the use of HAART, we developed two studies: the Observational Cohort Study (OCS) and the Viral Load Observational Database (VLODB). Both of these studies use information collected from patients’ medical records over a long period of time. To date, we have utilized the OCS and the VLODB to learn more about how patients are treated in relation to federal guidelines and the durability of viral suppression.

Overall Methods

Over 800 HIV positive patients at ten primary care sites in the San Francisco Bay Area consented to participate in the OCS or the VLODB. Research staff abstract data—including demographic characteristics, the patient’s lowest CD4+ cell count, highest viral load, and most recent laboratory test results, past and current antiretroviral treatment (ART), and history of opportunistic infections and malignancies—from patients’ primary medical record every four to six months. Data collected at follow-up include laboratory test results since the last abstraction, start and stop dates of ART, and any emergent opportunistic infections or malignancies.

• Clinical Guidelines and Clinical Effectiveness in HIV Care

Since the early 1990’s, the federal government has used emerging knowledge of HIV disease to formulate treatment guidelines for the care of HIV positive individuals. Despite the enormous effort to develop and disseminate these clinical guidelines, we have little information on how medical providers utilize them. Nor do we know whether care differs by gender, ethnicity, or mode of HIV transmission. Most importantly, we do not know whether patients in primary care who are treated according to the latest clinical guidelines actually have better outcomes than patients who are not.

Methods

To address these questions, we identified patients who might have considered HAART therapy based on the most aggressive aspects of the January 2000 “hit early, hit hard” clinical guidelines. This included patients who had a prior opportunistic infection or malignancy, or ever had a CD4+ cell count less than 500 (cells/mm³) or a viral load of greater than 20,000 (copies/mL PCR). For patients who were not on HAART, we identified those who were appropriate candidates to begin HAART based on less aggressive aspects of the clinical guidelines: patients with current CD4+ cell counts under 350 or viral loads over 20,000. For patients who were on HAART, we identified those for whom it was appropriate to change their HAART regimen due to virologic failure, defined as viral load exceeding 5000.

Findings

Of the 765 patients for whom data has been collected, 89% were male, 10% female, and 1% transgendered (male to female). The mean age was 44. About half (52%) of patients were Caucasian, 21% Latino, 19% African American, 3% Asian or Pacific Islander, and 4% of mixed or other heritage. The largest risk category for HIV was men who had sex with men (72%), followed by patients with prior injection drug use (18%), and patients who reported heterosexual sex as their primary risk (9%).

Overall, patients in the study had fairly advanced HIV disease; however, their current health status appeared quite good. Eighty-four percent had an AIDS diagnosis, 72% had a prior opportunistic infection or malignancy, and 55% had a CD4+ cell count of less than 200 at some time in the past. Mean current CD4+ cell count was 435. About half (48%) of patients had viral loads less than 500 at baseline, 23% had viral loads between 500 and 10,000, and 30% had viral loads of 10,000 or more.

Use of HAART

Most study participants (61%) were on HAART at baseline, 5% were on nucleoside reverse transcriptase inhibitors only, and 34% were not on ART. There were no differences in the proportion of patients on HAART by age, gender, ethnicity, HIV risk category, or CD4+ cell count at study entry. Patients on HAART did have lower viral loads at study entry, lower nadir CD4+ cell counts, and more likelihood of

having a prior opportunistic infection or malignancy compared to those not on HAART.

When to Start

Among the 309 individuals not on HAART at study entry, 227 (73%) were appropriate to start HAART based on their current health status (CD4+ cell counts less than 350 or viral loads over 20,000). There were no differences in age, gender, ethnicity, or HIV risk category in the proportion of patients appropriate to start HAART. As expected, patients who were appropriate to start HAART according to current guidelines had lower nadir CD4+ cell counts than those who were not appropriate to start HAART.

These results indicate that the majority of patients who are appropriate to begin HAART based on clinical guidelines appear to be treated according to the guidelines. However, a significant proportion of patients (approximately 25%) does not appear to be treated according to the guidelines. There are several possible explanations for this finding. Some patients may choose not to take ART, may delay taking ART until after they experience clinical symptoms of disease progression, or may stop taking ART because of drug side effects. Alternatively, some physicians may delay treatment because they do not agree with clinical guidelines, or because they believe that some of their patients will not be able to adhere to a HAART regimen.

When to change

According to clinical guidelines, patients who have viral loads greater than 5000 should consider changing their HAART regimen. One-quarter of those on HAART in our cohort fall into this category. Among the 464 patients on HAART at study entry, 112 (24%) were identified as virologically failing their regimen based on their current viral load (over 5000). The group with increased viral loads was younger than the group who was not failing (66% vs. 51% less than 45 years of age). There were no other demographic differences between the groups. Current CD4+ cell counts and nadir CD4+ cell counts were lower among those with virologic failure.

Physicians may be delaying changes in HAART regimens because many patients continue to feel well and to have stable CD4+ cell counts even after their viral loads become detectable. There also may be differences in adherence to HAART regimens among younger vs. older patients.

• Viral Load Observational Database

As protease inhibitors became available in early 1996, providers rushed to prescribe HAART to their patients. HAART was shown to reduce viral loads to undetectable levels. However, providers had little information on how long their patients' viral loads might remain undetectable or which of them might be likely to sustain undetectable viral loads for an extended period of time. To address these questions, we developed the Viral Load Observational Database (VLODB) to follow patients whose viral load became undetectable as a result of initiating HAART.

Methods

Population

Patients were selected if they had a previously detectable viral load of greater than 1500 and sustained a drop in viral load to less than 500 (“undetectable”) within 120 days of initiating HAART.

Sample

Among the 291 patients identified, 252 (87%) had at least one follow-up visit. Median follow-up was 22 months. The majority of patients were male (98%), Caucasian (74%), and men who had sex with men (83%).

Findings: Durability of Undetectable Viral Load

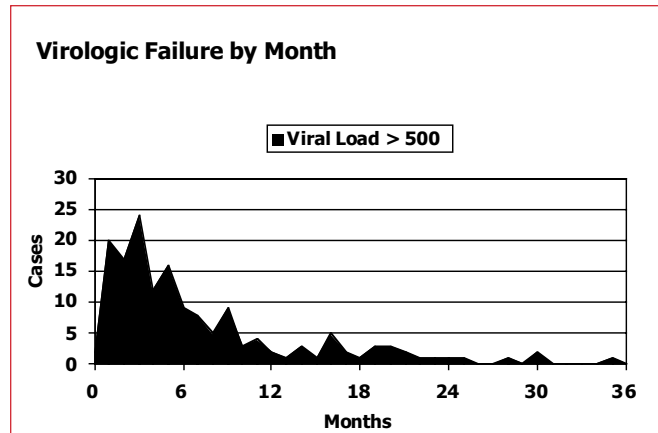
Estimates of the length of time that viral load would remain undetectable varied with the duration of follow-up. After our initial look at the data (at 7.5 months), only 38% of patients were predicted to remain undetectable for one year after initiating HAART. However, after 22 months of follow-up, 81% of patients were predicted to remain undetectable at one year.

Predictors of an increase in viral load within six months of becoming undetectable included prior exposure to antiretroviral medications, higher viral load prior to ART, and CD4+ cell count less than 200 prior to treatment. In addition, patients who changed their ART while their viral load was undetectable were more likely to experience a subsequent increase in viral load.

The difference in estimates of how long people would remain undetectable was due to the fact that many people experienced increases in their viral load during the first six months after becoming undetectable, whereas very few people experienced such increases after the first six

months (Figure 1). Therefore, early estimates of virologic failure after short periods of follow-up led to extremely pessimistic predictions of the effectiveness of HAART. Longer follow-up is necessary to gain a full picture of virologic failure in people on HAART.

Figure 1



What We Have Learned

- It is important to study the effectiveness of HAART and the appropriateness of clinical guidelines for the care of HIV positive patients in the community-based clinics where the majority of people with HIV receive their care. Long-term studies should seek to study patients that reflect the overall population of people with HIV in primary care settings.
- Many providers and patients do not follow the clinical guidelines for the care of people with HIV. However, patients continue to do well clinically. It will be important to follow patients over a long period of time to determine whether treatment in accordance with the guidelines provides the best care for patients with HIV.
- Among patients who virologically fail their HAART regimens, most fail within the first three to six months after initiating therapy. Long-term success of HAART is linked to viral load and CD4+ count prior to HAART as well as the prior treatment experience of patients. Additional follow-up will be necessary to understand fully the relationship between viral load, CD4+ cell counts, and clinical outcomes.

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Materials Available

The Community Consortium is happy to share information about its Observational Cohort Study. Write to Starley Shade at Community Consortium, Positive Health Program, AIDS Research Institute, University of California, San Francisco, 3180 18th Street, Suite 201, San Francisco, CA 94110, or email: sshade@php.ucsf.edu.