

PRIMARY (ACUTE) INFECTION

CHARACTERISTICS AND DIAGNOSIS OF PRIMARY INFECTION

1. To diagnose primary infection, expensive laboratory tests will probably need to be ordered. Given the expense, which test should we order? p24 antigen? Plasma HIV RNA?

Dr Richman: Within several days of infection, all patients will probably have a positive test for plasma HIV RNA for life in the absence of potent chemotherapy. A plasma HIV RNA test (either by RT PCR or the second generation branched DNA [bDNA] assay) is thus almost completely sensitive and specific. The p24 antigen assay is equally specific and less expensive. It will be positive during primary infection most of the time, but not always. Thus, a plasma HIV RNA test would be the quickest and simplest approach to diagnose primary infection. A less expensive approach may be to get a p24 assay; a positive result is diagnostic, but a negative result would require a plasma HIV RNA assay for confirmation.

2. In acute infection, does dissemination of HIV-1 seed out to sites other than lymph nodes?

Dr Richman: During primary infection, HIV replication is established in the lymphoid tissue, the central nervous system, and the genital tract (where high levels of virus shedding and transmission can occur).

3. When you consider latently infected CD4+ cells during primary infection, how can eradication be even theoretically possible using currently known therapeutics?

Dr Richman: If cells become latently infected during primary infection, then eradication is only theoretically possible if the latent cells have a finite lifespan (in contrast to ganglionic neuronal cells with herpes simplex virus or varicella-zoster virus infection) and if chemotherapeutic suppression is maintained until the latently infected cells expire and are replaced. Whether these theoretical possibilities prove to be the case requires systematic investigation, which is now under way.

INITIATING TREATMENT FOR PRIMARY INFECTION

4. Would you treat an at-risk patient (eg, a young gay man) presenting with compatible clinical syndrome (eg, aseptic meningitis) with anti-HIV therapy before test results are available? Most practice settings have more than 2-week delays for p24 or HIV RNA tests.

Dr Saag: Ideally, individuals with acute infection should be treated as early in the clinical course as possible in order to achieve maximum clinical benefit. The difficulty is not so much determining when to treat, but whether to treat at all. The decision to treat a probable but not confirmed case involves a difficult risk/cost analysis, which would sway one to treat only if one's confidence were fairly high. Because the acute HIV syndrome is not specific with regard to clinical presentation, presumptive therapy may often be directed at non-HIV symptoms. In the situation described, I would favor treatment initiation, pending the results of virologic testing.

The decision to treat early is based on pathophysiologic data and, to a large degree, clinical intuition, to protect uninfected cells from becoming infected at a time when the virus is spreading rapidly throughout the body (eg, brain, testes, gut). Through aggressive antiretroviral therapy, it is theoretically possible to prevent or minimize spread of the virus to these tissues. Moreover, at the time of initial infection, a single genotype (strain) of the virus predominates. Within 2 to 4 weeks after initial infection, that viral strain has begun to generate genetic variants, which provide an opportunity for the virus to escape selective pressure from drug therapy. By treating very early and aggressively, viral replication can be minimized, thereby minimizing the likelihood of development of resistant viral virions over time.

REGIMENS FOR PRIMARY INFECTION

5. What do you think of using NNRTIs early on as an additional strategy?

Dr Saag: The NNRTIs are especially attractive potential drugs for primary infection because they do not require the cellular processing to become active antiretrovirals (as is required for nucleosides, for example, which require cellular phosphorylation). In addition, the NNRTIs achieve high serum and cellular concentrations very early after the

initial dosing and are therefore especially attractive for primary infection as well as acute exposure (eg, after a needle stick injury in health care workers). The use of NNRTIs in combination with protease inhibitors should await results of studies assessing the safety and pharmacologic interactions of such combinations.

Dr Montaner: Although it is premature to characterize the best time to use NNRTIs, the nevirapine experience provides important clues in this regard. I generally favor the inclusion of NNRTIs in a 3-drug regimen when at least two (if not all three) of the drugs are new to the given patient. This approach applies regardless of disease stage. Until further data are available I would tend to favor the inclusion of NNRTIs within combination therapy regimens aimed to fully suppress viral replication. NNRTIs are relatively "fragile" compounds in that high levels of resistance require only one mutation, and for this reason full suppression of viral replication is necessary to protect their anti-retroviral effect.

6. What do you think about adjuvant use of immunotherapy during primary infection?

Dr Saag: The term immunotherapy represents a vast array of possible treatments ranging from immune stimulation (eg, interleukin-2) to immune suppression (eg, prednisone or cyclosporin). In view of our very limited knowledge of the nature of the immune response during acute infection, it is probably not wise to introduce immunotherapy of any sort during this period. The rationale behind the use of antiretroviral therapy is based in large degree on a fairly deep understanding of HIV pathogenesis and its relationship to viral replication. We do not have a comparable understanding of the immune response to HIV and interventions are as likely to do harm to a patient as good.

HOW LONG SHOULD TREATMENT FOR PRIMARY INFECTION CONTINUE

7. How would you manage a patient with acute infection if measurement of viral load is not available to you? After deciding to initiate therapy for primary infection, can one ever stop administering the drug?

Dr Saag: In most instances, the goal of treatment is to minimize the immune system destruction, and to maximize viral suppression, thereby minimizing the likelihood of development of drug resistant isolates over time. In such instances, therapy might best continue throughout the entire course of infection. If the rationale to initiate treatment was to completely eradicate HIV from an individual, then it would make sense to stop therapy at such time that the clinician believes that the goal of eradication has been

achieved. At present, however, it remains uncertain whether such a result can be achieved. It is speculated that it will take at least 2 to 4 years of chronic, aggressive suppressive therapy, to achieve this objective, if at all. Moreover, viral load measurements would be necessary in this strategy in order to demonstrate complete suppression (undetectable viral levels) for an extended period of time. In my opinion, in most instances, chronic viral suppression should be continued throughout the course of infection regardless of whether viral load measurements are available. A practical approach, if suppression is attained, would be to continue therapy and closely follow new developments in this rapidly changing field.

OTHER ISSUES

8. Why not use "virograms" to determine the resistance mutations of the recently-infected person?

Dr Katzenstein: Practical assays of reasonable expense to assess drug susceptibility or resistance mutations are not yet available. In most situations, it is currently easier and faster, and, perhaps, more relevant to evaluate the plasma HIV RNA response of the patient than to test his or her virus isolate for susceptibility or genetic sequence.

There are a number of in vitro techniques that are being developed to assess drug susceptibility. The use of the term "virograms" suggests use of viral sensitivity testing in which phenotypic susceptibility (analogous to the susceptibility testing for bacteria in the microbiology lab) is determined on an isolate or a recombinant virus derived from the patient. This is being developed, and is available as a research tool from a few laboratories. In addition, genetic sequencing from plasma HIV RNA is being explored as a method to detect resistant genotypes in the circulating virus population. These are both important epidemiologic tools. For example, they have been used to describe an increasing frequency of zidovudine-resistance mutations among isolates from seroconverters. However, in practice the value of this type of testing may be greatest when we have a clear understanding of the meaning of the results and have additional drug strategies that can be guided by such an approach. The presence of circulating virus, which is necessary for testing, already provides evidence that current drugs have failed.