

National AIDS Treatment Advocacy Project

Consensus Statement on 1592 Expanded Access and Accelerated Approval

Overview

Access to Glaxo Wellcome's 1592U89 now in development, potentially represents the only viable option for delaying disease progression for many people living with HIV and AIDS who have exhausted the benefit from currently approved antiviral therapies. In early clinical studies, 1592 has demonstrated a more potent level of antiviral activity than other RT inhibitors, with minimal side effects. Its most important property, however, is that people have not previously been exposed to it and it therefore offers the hope of renewed antiviral activity. This renders the drug critically important to two patient populations: (1) those who have already lost sensitivity to the other drugs of this type, and (2) those who need to use at least one fresh or new nucleoside analogue RT inhibitor to make reasonable use of combination therapy with protease inhibitors or non-nucleoside RT inhibitors. Existing evidence clearly suggests that combining such drugs with previously used therapies diminishes their effectiveness and leads to more rapid development of resistance.

The benefit of this drug may be limited due to the development of resistance, a problem common to all currently approved antiviral compounds. While it may take years of additional study to determine its optimal use, this should not delay prompt access to this therapy by people in immediate need. Delaying the availability of this drug until Phase III trials are fully accrued is unacceptable and represents a significant change from past practices. For example, the ddI, d4T, and AZT expanded access programs all took place while trials were still recruiting. We are very concerned that the recent activities of several pharmaceutical companies represents a broad effort to minimize the number of patients served by expanded access programs. Any such effort around 1592 would be a moral affront to the rights and needs of people with HIV/AIDS and their healthcare providers.

We hereby propose the following 1592 expanded access program, to be phased in in stages, with immediate access to those in urgent need.

First Phase - Compassionate Use/Salvage Therapy. Glaxo Wellcome and the Food and Drug Administration must cooperate and take a more compassionate stance to make this promising compound immediately available in a salvage program once a recommended dosing schedule has been established. This compassionate access/salvage program should make drug available as soon as possible for those people who have failed existing therapies and risk near-term danger of death or life-threatening infections.

The development of this drug must take into consideration its unique potential to provide benefit to the acutely compromised segment of the HIV-infected population. Availability of salvage strategies is of the highest priority for people living with HIV. There is no logical or moral reason to withhold this drug from people with advanced illness, people whose lives hang in the balance. Currently, this compound qualifies, by any humane standard, for compassionate use.

This first phase of Compassionate Use/Salvage Therapy should provide 1592 without delay to patients who meet any one of the following two requirements:

1. CD4+ Cell Count under 50 OR Viral Load over 40,000 copies/ml AND Treatment Failure to approved RT Inhibitors AND at least one Protease Inhibitor;
2. Diagnosis of AIDS Dementia Complex (ADC), unresponsive to existing therapies.

We believe evidence of the above conditions can be accomplished with a minimal amount of paperwork. A physician's letter accompanied by one lab report should be sufficient to establish any of the above criteria.

Second Phase - Expanded Access. This second phase of Expanded Access should provide 1592 during recruitment and conduct of Phase II/III clinical trials, but no later than ninety (90) days from the start-up of the First Phase, to patients who meet any of the following criteria:

1. Patients who do not qualify for or are denied entry in a 1592 clinical trial and have a medical need for 1592, or
2. Patients who do not live within a radius of 15 miles of an active clinical trial site, or
3. Patients whose lives would be immediately jeopardized by randomization to an ineffective treatment regimen, or
4. Patients with a CD4+ Cell count below entry requirements of clinical trials, or
5. Viral Load greater than 20,000 copies/ml., despite use of currently approved therapies, or
6. Treatment Failure or demonstrated genotypic or phenotypic resistance to approved RT inhibitors.

Accelerated Approval. This compound should be licensed for accelerated approval as soon as possible. FDA approval of this compound should be based on existing regulations governing accelerated approval of new drugs for life-threatening illnesses:

1. Clear evidence of benefit on surrogate markers have been demonstrated;
2. Principal toxicities and drug interactions have been defined;
3. Longer-term development plans have been initiated designed to determine the drug's usefulness in promoting clinical and survival improvements and durability of response, as part of a medical strategy for coping with HIV infection.

We urge the sponsor to file applications for accelerated approval no later than the 3rd quarter of 1997.

Resistance, Pharmacokinetics and Drug Interactions. As with all antivirals, the development of drug-resistant strains of virus, drug interactions and pharmacokinetic variances while using this compound may warrant additional considerations. To address this concern, sponsors should also be required, prior to accelerated approval, to present meaningful data on:

1. the speed and levels of resistance encountered;
2. the degree of cross-resistance found with other nucleoside analogues;
3. the interaction of the compound with other commonly used anti-HIV medications;
4. bioavailability in men, women, and children and determination of the degree which blood levels vary depending on body weight.

Summation Any effort to withhold access to promising compounds is contrary to the interests of HIV-infected people, inconsistent with the Accelerated Approval regulations, and scientifically unwarranted. The long history of the development of the earlier generation of antiviral drugs clearly demonstrates that it is possible to accrue patients and continue conducting clinical trials of compounds, long after their marketing approval. Because of the issues of drug resistance and drug failure over time, new therapies for HIV disease will continue to play a critical role no matter how many drugs become available on the market. New therapies, like 1592, must continue to be made available as rapidly as possible to patients with immediate needs for changed or improved treatment.

AGREED and ACCEPTED this ____ day of _____, 1996:

By: _____

Of: _____

Signature

Organization

Print Name: _____

If you and/or your organization would like to sign on to this statement, you can download it or copy it and fax it to (310) 471-4565. If you need a separate copy you can fax a request to the same fax number.

Commentary from Jules Levin: There are many individuals who are not now benefitting from protease inhibitor therapy. They may have rebounded due to resistance or for some other reason are not responding well. These individuals need access to therapy that will help them. At this point in time, we know that if you are failing a regimen or have been on a regimen for a prolonged period of time, merely adding one new drug (no matter how potent it is) may not serve you well in the long run. Therefore, if you are able to access 1592, it would serve you well to consider adding a second new drug to therapy. You can consider adding a NNRTI like nevirapine or delavirdine; or, possibly nelfinavir if you access it through Agouron's expanded access.

If you can wait until 1592 is available and there is more data, you might be better served to do that. One concern is that we don't yet know how effective 1592 will be for individuals who are resistant to RTIs like AZT, 3TC, d4T and ddI. A Glaxo study is now recruiting to explore that question. It is for protease-naive but RTI-experienced individuals. Data from that study should address the question of resistance.

Glaxo should make this drug available to individuals truly in need. Those who are failing protease inhibitors and who are doing poorly, and want access should have the opportunity. But, remember if not used properly and resistance develops, you will lose the possibility of benefiting from it later in a potentially more effective combination.

Ideally, Glaxo should provide an access program for these individuals that would provide 1592 in combination with their new protease inhibitor now in development (VX-478, 141W94). That would offer a better opportunity for individuals to properly benefit. This would offer two new drugs.

Please e-mail any comments you may have to me at JuLev@aol.com