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January 13, 2006

Mr. David Zentner, Director  
Medical Services, DHS  
600 E. Boulevard Avenue  
Bismark, ND 58505

**RE: Implementation of TAR Procedures for HIV Drug Trizivir**

Dear Mr. Zentner,

In light of recent clinical trial results, AIDS Healthcare Foundation would like to re-submit our request for treatment authorization request ("TAR") procedures to be placed on Trizivir, a product used to treat HIV/AIDS.

Our original request was based on the interim results from the Adult AIDS Clinical Trial Group (AACTG) 5095 study. The study was a comparison between Trizivir alone, and a four-drug (Trizivir + efavirenz) and a three-drug (Combivir + efavirenz) regimen. It revealed that subjects given Trizivir alone experienced accelerated virologic failure. To minimize the hazardous effects on subjects, these interim results led to discontinuation of the Trizivir-only arm of the trial, as well as a "Notice to Physicians" from the National Institute of Allergy and Infectious Diseases citing the dangers of prescribing Trizivir as a stand alone therapy in treatment naïve patients.

In December 2005, final results for AACTG 5095 revealed still more information regarding patient response to Trizivir, in this case in combination with efavirenz. Dr. Gulick's study revealed no additional benefit from the use of the four-drug regimen (Trizivir + efavirenz) when compared to the three-drug regimen (Combivir + efavirenz). *"After a median of 3 years of follow-up, the 3-drug efavirenz regimen proved similar to the 4-drug efavirenz combination with regard to virologic failure rate, time to virologic failure, CD4+ cell count gains, and frequency of grade 3 or 4 side effects."*

The AACTG 5095 final results underscore the need for TAR procedures to be placed Trizivir, given the drug's ineffectiveness. We continue to be concerned that physicians not expert in HIV medicine may continue to prescribe it to naïve patients, and that such prescriptions will have an adverse fiscal impact on the state.

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For the above reasons, AHF, a non-profit organization that provides HIV/AIDS medical services to some 17,000 people in the United States, requests that California place appropriate TAR procedures on Trizivir for ARV naïve patients. By implementing these procedures, you would ensure that treatment naïve patients receive Trizivir only when absolutely medically necessary, and guarantee that better medication regimens are used for the vast majority of patients (thereby increasing health outcomes and maximizing the value of state Medicaid expenditures). At the same time, Trizivir would continue to be readily available for patients already taking HIV/AIDS medications.

Thank you for your attention in this matter. If you have any questions, or require additional information, please do not hesitate to contact my office at 323-860-5200. I look forward to hearing from you.

Sincerely,



Michael Weinstein  
President

Cc: Ms. Karin Mongeon, North Dakota State ADAP Director

# AIDS HEALTHCARE FOUNDATION

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October 21, 2004

Mr. David Zentner  
Director  
Medical Services, DHS  
600 E. Boulevard Avenue  
Bismark, ND 58505  
(701) 328-1544

RE: Implementation of TAR Procedures for HIV Drug Trizivir

Dear Mr. Zentner,

This is to request that the North Dakota Medicaid program place treatment authorization request procedures ("TAR") on Trizivir, a product of GlaxoSmithKline ("GSK") used to treat HIV/AIDS.

Based on recent tests and studies, AIDS Healthcare Foundation ("AHF"), the nation's largest AIDS treatment organization believes that Trizivir, a fixed dose combination drug containing three separate medications used to treat HIV/AIDS, is not appropriate in most cases for treatment naïve HIV patients. We are concerned that physicians not expert in HIV medicine may continue to prescribe to naïve patients, and that such prescriptions will have an adverse fiscal impact on the state.

We therefore urge that the TAR process be implemented to restrict Trizivir's use for patients who are naïve to ARV therapy.

Trizivir is a fixed dose combination ("FDC") tablet that contains the following HIV/AIDS medications: AZT, 3TC, and abacavir. One of the presumed benefits of Trizivir - taking these three drugs in one pill - is that, because it purportedly lowers the pill burden, there will be better compliance and adherence to a medication regimen. This, the theory goes, will result in increased health outcomes for patients, as well as increased ease of use and treatment by doctors. For these reasons, FDC products have experienced a growth in use and popularity and are now produced in various forms by a number of pharmaceutical companies.

The problem with Trizivir is that, while the individual medications comprising it may be effective in treating HIV/AIDS, the specific

# AIDS HEALTHCARE FOUNDATION

combination has been shown to have minimal effectiveness. The National Institutes of Health ("NIH") conducted a study to measure the effectiveness of various AIDS drug combinations, including Trizivir (ACTG 5095). In March of 2003, however, the NIH suspended a portion of its study comparing Trizivir to other regimens.

The NIH study compared treatment naïve patients on Trizivir alone with patients who took a combination of Trizivir and Bristol-Myers Squibb Co.'s ("BMS") Sustiva, or Sustiva and a two-drug tablet called Combivir, also made by GSK. Twice the number of Trizivir-only patients saw their HIV levels climb again within about eight months of starting therapy. According to a Kaiser Daily HIV/AIDS Report on the issue, the researchers stopped one arm of the study because patients taking Trizivir experienced virologic failure - defined as having a viral load level above 200 copies/ml at least four months after beginning the treatment—sooner and more often than patients in the other two arms of the study.

The finding that Trizivir is less effective for treatment naïve patients with HIV/AIDS recently was stated again in a study published in the April 29, 2004 issue of *The New England Journal of Medicine* (Volume 350, Number 18, pages 32-43).

Trizivir's lack of effectiveness renders it unsafe for treatment naïve patients. It is apparent that Trizivir may be effective only if it taken with other HIV/AIDS drugs. However, Trizivir is marketed and used to treat HIV alone. The potential harm to these patients is increased as many are treated by general practitioners who may not be aware of the most recent findings and continue to prescribe Trizivir to treatment naïve patients. This will result in reduced health outcomes for those who take the promise of the FDC to heart and use only Trizivir.

While Trizivir may be effective when taken in combination with other HIV/AIDS medications, the necessity of taking additional medications appears to defeat the purpose and benefit of fixed dose combination therapy - reducing pill burden to increase regimen adherence and compliance. Therefore, the chief benefit of Trizivir is lost.

The end result of the continued presence of Trizivir on the market is confusion, decreased health outcomes, and drug resistance. Given the effectiveness of the three drugs comprising Trizivir, and the existence of numerous other AIDS medications, including other FDC's, the continued use of Trizivir for treatment naïve patients presents a real danger to those people afflicted with HIV/AIDS.

For the above reasons, AHF, a non-profit organization that provides HIV/AIDS medical services to some 12,000 people in the United States, requests that your state place appropriate TAR procedures on Trizivir for ARV naïve patients. By

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Implementing these procedures, you would ensure that treatment naïve patients receive Trizivir only when absolutely medically necessary, and guarantee that better medication regimens are used for the vast majority of patients (thereby increasing health outcomes and maximizing the value of state Medicaid expenditures). At the same time, Trizivir would continue to be readily available for patients already taking HIV/AIDS medications.

Thank you for your attention in this matter. If you have any questions, or require any additional information, please do not hesitate to contact my office at 323 860 5200. I look forward to hearing from you.

Sincerely,



Michael Weinstein  
President

Cc: Ms. Karin Mongeon, North Dakota ADAP Director

Print Page

## News Report

## Final results from ACTG 5095 report no additional benefit from use of 4-drug vs 3-drug efavirenz-based regimen in first-line therapy

December 16, 2005

First-line therapy with abacavir, efavirenz, and fixed-dose zidovudine/lamivudine did not control HIV replication better than the latter 3 drugs alone in a double-blind, placebo-controlled trial. This conclusion was drawn from AIDS Clinical Trials Group (ACTG) study 5095 and reported at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC.<sup>[1]</sup>

In 2003, a review panel stopped 1 of the treatment arms of this trial—a nucleoside-only arm consisting of abacavir/zidovudine/lamivudine—because of inferior virologic response relative to that observed in a pooled analysis of the 2 efavirenz-containing regimens.<sup>[2]</sup>

After a median of 3 years of follow-up, the 3-drug efavirenz regimen proved similar to the 4-drug efavirenz combination with regard to virologic failure rate, time to virologic failure, CD4+ cell count gains, and frequency of grade 3 or 4 side effects. Black patients had a higher risk of failure than whites or Hispanics, a finding that did not appear to be related to differences in adherence between the 3 groups.

Roy Gulick, MD, of Cornell University, and ACTG colleagues tested the 3 regimens in antiretroviral-naïve patients with viral loads  $\geq$  400 copies/mL and any CD4+ cell count. After the triple-nucleoside regimen was closed, the ACTG team continued to follow 765 patients randomized to either of the 2 efavirenz arms. Participants in these groups began therapy with similar viral loads (averaging 72,444 copies/mL) and CD4+ cell counts (averaging 240 cells/mm<sup>3</sup>). Fifty-seven per cent of participants had a viral load < 100,000 copies/mL at baseline.

After a median of 144 weeks of follow-up, Dr. Gulick and colleagues found no difference between the 4-drug regimen and the 3-drug regimen with regard to the trial's primary endpoint—the proportion of patients with a confirmed viral load > 200 copies/mL at study Week 16 or later: 99 (26%) taking efavirenz/zidovudine/lamivudine and 94 (25%) taking efavirenz/abacavir/zidovudine/lamivudine met that failure definition.

Time to virologic failure did not vary between treatment arms, either in the whole study population or after stratification for baseline viral load above or below 100,000 copies/mL. Time to treatment discontinuation and the proportions of study participants who achieved a viral load < 50 or 200 copies/mL also proved similar in the 2 groups. More than 80% of patients in each study arm maintained a viral load < 50 copies/mL throughout follow-up in an intent-to-treat analysis. CD4+ cell counts increased by 250-300 cells/mm<sup>3</sup> with both the 3-drug regimen and

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the 4-drug regimen.

Multivariate analysis identified 2 factors that predicted virologic failure: Blacks had a 1.67 times higher risk of virologic failure than whites (95% confidence interval: 1.19-2.35;  $P = .0003$ ), and HCV coinfection increased the risk of failure 1.57 times (95% confidence interval: 1.02-2.40;  $P = .04$ ).

Blacks, whites, and Hispanics reported similarly high rates of adherence throughout the follow-up period, with approximately 85% saying they had not missed a dose in the past 4 days, a validated measure of antiretroviral adherence.

Earlier work indicated that blacks have a higher rate of genetic polymorphisms in genes that code for the enzyme which metabolizes efavirenz. Those genetic mutations have been correlated with higher efavirenz levels, which may cause more side effects. In fact, Dr. Gulick reported, blacks in ACTG 5095 did have a significantly shorter time to discontinuation of their assigned regimen and significantly higher rates of grade 3 or 4 side effects than did whites or Hispanics. However, he noted that this hypothesis explaining the higher risk of failure of these efavirenz regimens in black participants in study 5095 remains speculative.

#### References

1. Gulick R, Ribaudo H, Shikuma C, et al. ACTG 5095: zidovudine/lamivudine/abacavir vs. zidovudine/lamivudine + efavirenz vs. zidovudine/lamivudine/abacavir + efavirenz for initial HIV therapy. Program and abstracts of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy; December 16-19, 2005; Washington, DC. Abstract H-416a.
2. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004;350:1850-1861.

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