Efficacy of Tenofovir as Intensification of Zidovudine/Lamivudine/Abacavir Fixed-Dose Combination in the Treatment of HIV-Positive Patients

Coformulated zidovudine/lamivudine/abacavir fixed-dose (ZDV/3TC/ABC-FDC; Trizivir, GlaxoSmithKline) has been widely used because of its convenience, tolerability, and simplicity. It also offers the possibility of reserving both the protease inhibitor and nonnucleotide reverse transcriptase inhibitor classes (NNRTIs).

Based on the ACTG 5095 trial, this combination was found to be less effective than 2 efavirenz-based regimens at all viral load strata.[1] As a result, it has been recommended to intensify such regimens. We chose to intensify with tenofovir in a number of cases, and we now report our results with this strategy.

An analysis of patients taking Trizivir, 1 pill twice a day with HIV viral load of <1000 copies/mL but >50, who had tenofovir 300 mg once daily added to their regimen for intensification was performed retrospectively.

Fifteen patients (12 male) were identified. Patients were receiving current Trizivir twice a day prior to adding tenofovir for an average of 10 months. The combination of Trizivir plus tenofovir was well tolerated and no patients discontinued the treatment due to an adverse event. Table 1 and Figure 1 summarize the findings.

At week 24, 11 of 15 (73%) of the patients had achieved HIV RNA <50 copies/mL, compared with 2 of 15 (13%) at baseline, with a mean $\log_{10}$ decline of 1.33 in HIV RNA and a mean increase in CD4 of 66 cells/mm^3.

TABLE 1. Baseline and Follow-up Data

	Baseline (n = 15)	Week 12 (n = 15)	Week 24 (n = 15)
Mean CD4 Count (%) (range)	425 (23) [186–927]	443 (24) [174–931]	491 (25) [224–1032]
Mean HIV-RNA ($\log_{10}$) (range)	287 (2.02) [<50–879]	216 (1.43) [<50–694]	170 (0.69) [<50–872]
VL <400 copies/mL	12/15 (80%)	12/15 (80%)	12/15 (80%)
VL <50 copies/mL	2/15 (13%)	6/15 (40%)	11/15 (73%)

To our knowledge, this is the first study to look at intensification of Trizivir with tenofovir. Our results showed that adding tenofovir to Trizivir in patients with HIV RNA <1000 copies/mL can result in further decreases in viral load through 24 weeks. When Trizivir and tenofovir are started simultaneously, successful responses have been observed in treatment-experienced patients[2] and in patients who are antiretroviral naive.[3,4] In one study (COL40263), Trizivir and tenofovir were administered together in antiretroviral-naive patients as a once-daily regimen, with 76% of subjects experiencing an early virologic response after 8 weeks.[3] Virologic nonresponse was observed only in 8 of 54 subjects (15%) at 24 weeks of follow-up. In another recent study, the combination of Trizivir with tenofovir was found comparable to the regimen of ZDV/3TC (Combivir) and efavirenz in initial therapy for treatment-naive HIV-infected persons.[4] By intent-to-treat (ITT) analysis, 68% of patients on the quad-NRTI arm achieved HIV RNA levels of <50 copies/mL at 48 weeks, which was similar to the 67% result observed in patients receiving Combivir with efavirenz. Lastly, the combination of Trizivir with tenofovir has been used successfully in subjects with early virologic failure on a regimen of either ZDV or stavudine (d4T) given with 3TC and either a protease inhibitor or an NNRTI.[5] In this study, after 24 weeks of therapy, on ITT analysis, 65% of patients achieved HIV RNA of <50 copies/mL (80% of patients when an as-treated analysis was used).

The combination of Trizivir plus tenofovir as quad-NRTI therapy would have the potential to preserve future treatment options with other drug classes. Previous studies have indicated that ZDV may play a role in inhibiting the emergence of K65R.[6] A recent analysis of HIV-1 isolates in the Virco database pointed out to a bidirectional antagonism between the K65R mutant and thymidine analogue mutations.[7] Therefore, the presence of ZDV (a thymidine analogue) may preselect for thymidine analogue mutations and delay the emergence of K65R. Preliminary results from virologic failures in patients taking Trizivir plus tenofovir have supported this hypothesis as more patients developed thymidine analogue mutations than K65R.[3] However, this strategy is not without risks, leading perhaps to a broad NRTI cross-resistance.

In summary, this small data set suggests that intensifying therapy for

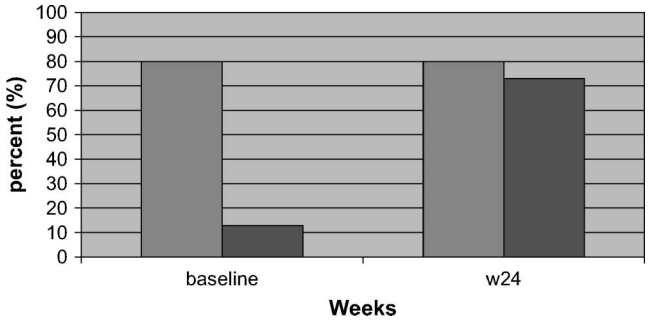

FIGURE 1. Percentage of patients with undetectable HIV-RNA (light gray: <400; dark gray: <50 copies/mL).

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patients in whom an initial regimen of Trizivir fails, with a viral load still <1000 copies/mL, using tenofovir is perhaps a reasonable therapeutic strategy. This approach offers the potential for improved potency while reserving other classes for future use. Before such a strategy can be recommended, however, its benefits and risks need to be evaluated in larger clinical trials.

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Cancer Prevention and Early Diagnosis in HIV-Positive Individuals

To the Editor:

Since highly active antiretroviral therapy (HAART) has been available in clinical practice, higher survival and life expectancy rates have been registered in the HIV-positive population, and as a result several chronic non-HIV-related conditions, like liver and cardiovascular diseases, have become more important in the clinical treatment of HIV-positive individuals. At the same time, we are faced by the challenge of an aging HIV-positive population. In recent years, age at the time of diagnosis of AIDS has progressively increased. In the United States, 10–15% of AIDS cases are found in individuals over 50 years of age and a consistent number of AIDS cases are being diagnosed in people over 65, especially in women. According to epidemiologic data, it is estimated that there are presently in the United States 60,000 HIV-positive individuals over 60 years of age.[1] In Italy, a recent survey has shown that the median age at AIDS diagnosis in adults has increased with time from 29 and 24 years in 1985, to 40 and 36, in 2002 for men and women, respectively.[2] In the general population, the most common tumors, eg, lung, breast, prostate, and colorectal cancer, increase exponentially over 50 years of age. Hence, the incidence rates of the most common types of cancer in the elderly can be expected to augment in the near future, as HIV-positive individuals grow older. With aging, a faster CD4 depletion has been shown in the literature,[3] and it can impair the cell-mediated immunity that helps fighting cancer. Moreover, behavioral non-HIV-related factors can intensify the risk of cancer, especially heavy long-term smoking. The increased risk for lung cancer in heavy smokers is well known; furthermore, smoking is a significant risk factor for other tumors, like head and neck, esophageal, pancreatic, and bladder cancers, and also for cardiovascular diseases. Other factors that may play a role in increasing the risk of cancer in HIV-positive patients are alcohol and coinfections from other oncogenic viruses like human papilloma virus and hepatitis B and C.

The impact of HAART on cancer incidence rates is still to be defined and the scenario of HIV and non-HIV-related neoplasms continues to evolve. A reduction in Kaposi sarcoma incidence cases has been reported by several authors using different study designs, while the effect of HAART on the incidence of non-Hodgkin lymphoma is less consistent, and the latter, as percentage of AIDS-defining illnesses, has increased since 1995.[4] Moreover the incidence of invasive cervical cancer in HIV-seropositive women has increased since the introduction of HAART.[5] HIV-infected patients are at significantly higher risk than the general population for some malignancies, such as Hodgkin disease and invasive anal cancer, as shown by recent cohort and linked AIDS–cancer registry studies. Non-AIDS-related neoplasms account for an increasingly larger proportion of deaths.[6] Among the most common malignancies in the elderly, the incidence of lung cancer is growing in HIV-infected subjects. Recent epidemiologic studies suggest a statistically significant elevated risk in HIV-infected subjects,[7–9] with an higher risk among IV drug users, a notoriously heavily smoking population.[9] Incidence rates of lung cancer exceed those in the general population.[10]

It is clearly established within the general population that screening and early diagnosis have reduced mortality rates from the most common forms of cancer significantly. The American Cancer Society screening and early diagnosis guidelines have been issued recently (Table 1).[11] As for lung cancer early diagnosis, the findings of the trials carried out so far are not satisfactory: the standard diagnostic screening has not reduced mortality rates significantly. The importance of spiral CT scanning in early diagnosis is still to be evaluated. The results of the Early Lung Cancer Action Project (ELCAP) show that spiral CT can identify small lung cancers in high-risk individuals, with a resectability rate of 96% and a proportion of stage I tumors >80%.[12] Moreover, low-dose spiral CT combined with selective use of positron

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TABLE 1. American Cancer Society Guidelines

Cancer	Population	Test or Procedure	Frequency
Breast	Women age > 50 y	Breast self-examination	Every month, starting at age 20
		Clinical breast examination	Every 3 y, from 20 to 39 y; yearly over 40 y
		Mammogram	Yearly over 40 y
Colon-rectum	Men and Women age > 50 y	Fecal occult blood test	Yearly
		Sigmoidoscopy	Every 5 y
		Fecal occult blood test + sigmoidoscopy	Yearly fecal occult blood test and sigmoidoscopy every 5 y
		Double contrast barium enema	Every 5 y
		Colonoscopy	Every 10 y
Prostate	Men age > 50	Digital rectal examination and prostate-specific antigen test	Yearly

emission tomography can effectively detect early lung cancer in the general population.[13]

The problems connected with non-HIV-related cancer early diagnosis methods and procedures have not been addressed, and so far no recommendations for early diagnosis of the most common forms of neoplasia have been suggested. Cancer prevention cannot rule out the reduction of risk factors: the first measures to be taken to prevent the occurrence of cancer involve prevention and among them tobacco control. Furthermore, the compliance of HIV-positive individuals with early diagnosis programs must be evaluated: screening is now available for a population cohort before the occurrence of the disease symptoms. Hence, it is mandatory to minimize the discomfort induced in the vast proportion of individuals undertaking screening, who will not benefit from these procedures. A high-quality standard must be assured throughout the screening program.

At the Aviano Cancer Center, HIV-positive patients are enrolled in screening and early diagnosis programs according to American Cancer Society guidelines and a lung cancer early diagnosis clinical trial using spiral CT and positron emission tomography is ongoing.

We believe that, with the aging of HIV subjects, a comprehensive approach cannot do without specific screening and early diagnosis programs. Time has come to investigate the relation among HIV infection, age, and cancer. These studies may produce new findings with reference to the natural history of HIV infection and give us new opportunities to improve the overall clinical treatment of HIV-positive individuals.

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