Hot News

Understanding the Changing Prevalence of K65R

Selection of the reverse transcriptase mutation K65R has been a matter of concern because the mutation may result in broad cross-resistance, reducing susceptibility to all other approved nucleoside reverse transcriptase inhibitors (NRTI), except zidovudine. The mutation is selected mainly by tenofovir (TDF) and to a lesser extent by didanosine (ddI) and abacavir (ABC). Despite the wide use of K65R-selecting drugs, the overall prevalence in treatment-experienced patients has been quite low. However, an increasing trend in prevalence and incidence has been observed in recent years, which is attributed to the increasing use of TDF since its FDA approval in 2001.

Remarkably, following this initial rise, in more recent years a decline in K65R incidence was observed despite a continuously increasing use of TDF (Camacho, et al. Antivir Ther. 2006;11:S134). Retrospective analysis of an HIV drug resistance database indicated that the initial rising prevalence of mutation K65R and the subsequent sharp decrease in selection rate were associated with a change over time in the use of additional drugs in combination with TDF, especially coadministration of ddI and ABC, and thus not solely attributable to the use of TDF itself. A similar decreasing trend was recently observed in a Spanish HIV/AIDS clinic (de Mendoza, et al. CID. 2008:46:1782). Similarly, in their study the K65R time trend again correlated with a decline in the prescription of TDF plus ddI or ABC, currently non-recommended combinations.

A number of thymidine-sparing nucleoside combinations have been associated with early virologic failure and an increased risk of K65R selection. As described above, the main determinants of K65R selection are combinations including TDF with ddI or ABC. However, additional drug classes other than NRTI seem to play an important role in the emergence of K65R. The K65R mutation is also common among patients receiving a combination of TDF and a nonnucleoside reverse transcriptase inhibitor (NNRTI). A possible epistatic fitness effect between K65R and the NNRTI mutation Y181C has been reported and could explain the increased selection of K65R (Deforche, et al. Antivir Ther. 2005:10;S144. Camacho, et al. Antivir Ther. 2006;11:S134). An association between NRTI and NNRTI mutations was also observed in a Swiss HIV Cohort Study, which detected a pattern between K65R, Y181C, and G190S (von Wyl, et al. CID. 2008:46;1299). This could explain why inclusion of a boosted protease inhibitor, instead of a NNRTI, to the combination of TDF and ddI appears to be protective against the development of K65R (Waters, et al. CID. 2008:46;96. Von Wyl, et al. CID. 2008:46;1299).

Because of the preferred use of TDF in first line, and because the selection of K65R will compromise any next-line NRTI backbone, it is vitally important that we understand the factors predisposing HIV for K65R selection. It seems that we are gradually getting there.

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Aids-Related Malignancies – A New Approach

At the beginning of the HIV pandemic, most complications in AIDS subjects were due to infectious diseases. After the introduction of HAART in 1996, survival dramatically improved in such a way that neoplastic diseases, mainly non-Hodgkin's lymphomas and Kaposi's sarcoma, are currently recognized in more than 40% of patients at some point in their lives. Besides these malignancies, the rate of other non-HIV related cancers have increased in recent years. Herein, I summarize the most important reports of malignancies at the 15th CROI, held in Boston in February 2008. The changing incidence of tumors in HIV patients has been acknowledged by the latest recommendations of the Spanish GESIDA/PETHEMA group, focused on diagnosis and treatment of AIDS-related lymphomas.

Several communications at CROI about AIDS-defining and non AIDS-defining cancers were reported. Zoufaly, et al. (abstract 16) analyzed the risk factors for development of malignancies and identified that incomplete viral suppression during HAART was a strong predictor for development of AIDS-related lymphomas. In this way, a clinical strategy of pursuing optimization of HAART at any time point with respect to viral suppression could help to minimize the incidence of AIDS-related lymphomas. Likewise, Bruyand, et al. (abstract 15) found that a longer exposure to uncontrolled plasma HIV RNA was associated with a higher risk of AIDS-defining cancers, regardless of CD4$^+$ counts. Moreover, they observed that prolonged immunosuppression was associated with a higher risk of any kind of cancers across all CD4$^+$ count strata. For all these reasons and in order

to prevent the occurrence of cancers, HAART should aim at reaching and maintaining CD4+ counts > 500 cells/mm^3. Of course, this consideration may force to switch current treatment guidelines, which do not recommend starting antiretroviral treatment until CD4+ counts go below 350 cells/mm^3.

The Spanish GESIDA/PETHEMA group has recently released recommendations for the diagnosis and treatment of AIDS-related lymphomas (Miralles, et al. Med Clin (Barc). 2008;130:300-11). There is important news in these updated guidelines, with the crucial role of neoplasm variables rather than HIV parameters being the best predictors of outcome. Accordingly, cancer treatment in HIV-infected persons on HAART should follow the same rules as in HIV-negative counterparts, and six cycles of CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) must be given for the treatment of non-Hodgkin's lymphomas. Although controversy persists about rituximab use in HIV patients, mainly due to enhanced risk of infections, Wyen, et al. (abstract 1026) confirmed that it significantly improves survival, even in severely immunocompromised patients. With respect to central nervous system (CNS) prophylaxis, as universally recommended in the past, it is currently advised that it only be given to subjects with the highest risk for developing neurologic disease, such as (i) patients with Burkitt's lymphoma, (ii) stage IV, and (iii) ORL lymphomas.

In patients with refractory or relapsed systemic lymphomas, the prognosis remains very poor. If the clinical situation is good and it is decided to proceed with salvage therapy, special consideration should be given to autologous hematopoietic cell transplantation. Treatment for CNS lymphomas has also experienced some changes, and the best results are obtained using HAART, glucocorticoids, and methotrexate, with or without craniospinal radiation. Although prognosis continues to be poor and median survival is only 1-3 months without therapy, survival may increase to 3-18 months with specific therapy.

There is an increased incidence of several other types of cancer in HIV-infected subjects. In one of the largest studies (Engels, et al. AIDS. 2006;20:1645-51), 563 non AIDS-related cancers were diagnosed in 375,933 HIV-infected persons. Lung carcinoma, Hodgkin's lymphoma, and anal neoplasia were the most frequent cancers. At CROI, Bruyand, et al. (abstract 15) reported 251 tumors in 4,194 HIV-infected patients. Interestingly, non AIDS-defining neoplasms were more frequent than AIDS-defining cancers (142 vs. 109 cases, respectively). Lung carcinoma is generally advanced at presentation, survival is poor, and incidence is increased even among non-smoker HIV-infected persons. HIV-associated Hodgkin's disease should be treated in the same way as in immunocompetent patients with six ABVD cycles (doxorubicin, bleomycin, vincristine and dacarbazine), as long as HAART, supportive therapy and prophylaxis for opportunistic infections is ensured (Xicoy, et al. Haematologica. 2007;92:191-8).

The current knowledge about HIV-related malignancies can be summarized in the next 10 essential points:

- HAART should aim at reaching and maintaining a CD4+ count > 500 cells/mm^3 to prevent the occurrence of all cancers.
- Most neoplasms in patients with HIV infection are linked to other viral diseases (Epstein-Barr virus and lymphomas, human herpes virus-8 and Kaposi's sarcoma, human papillomavirus and cervical/anal neoplasms, hepatitis C and B viruses, and liver cancer).
- Prophylaxis of opportunistic infections has to be done while patients are receiving chemotherapy, even when CD4+ counts are > 200 cells/mm^3.
- Factors related with neoplasms rather than HIV variables are the main predictors of treatment response and outcome.
- All HIV patients with lymphomas (Hodgkin's and non-Hodgkin's) have to be treated with HAART and chemotherapy simultaneously.
- As in HIV-negative counterparts, six cycles of CHOP-R should be recommended as treatment for non-Hodgkin's lymphomas. Likewise, six cycles of ABVD should be provided for treating Hodgkin's disease.
- Rituximab significantly improves survival of patients with HIV-related non-Hodgkin's lymphomas, without increasing mortality from infections.
- Central nervous system prophylaxis should only be done in subjects with the highest risk for developing neurologic disease, such as in patients with Burkitt's lymphoma, those with stage IV, and those with lymphomas of the ORL area.
- In HIV patients with refractory or relapsed lymphomas, if the clinical situation is good enough and it is decided to proceed with salvage therapy, special consideration should be given to autologous hematopoietic cell transplantation.
- In HIV-infected individuals, there is an increased incidence of several other types of cancer, mainly lung cancer and Hodgkin's lymphoma.

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New Resistance Score for Tipranavir

Along with darunavir, tipranavir is one of the two latest so-called second-generation protease inhibitors approved for the treatment of HIV infection. While the magic of darunavir is based on its strong affinity binding for the HIV protease, the basis for the strong potency of tipranavir resides in its non-peptidomimetic structure. In contrast, all other protease inhibitors resemble the natural protease substrates. In fact, recent evidences suggest that fosamprenavir and darunavir may share important amino acid positions for developing drug resistance (e.g. 50V), which may explain the expected lower response to darunavir after failing fosamprenavir.

At the 6th European Resistance Workshop held in Budapest, Hungary last March, new resistance scores for darunavir and tipranavir were released. Table 1 records the list of 11 mutations that currently seem to impact more on the virologic response to darunavir (de Meyer, et al. 6th European Resistance Workshop; Budapest, March 2008; abstract 54). When three or more of these mutations are present, the response to the drug is significantly compromised. As expected, some changes seem to reduce the susceptibility to darunavir more than others, and this is particularly the case for 50V, I54L, L76V, and I84V (see Table). Of note, these changes are often selected upon failure on fosamprenavir and lopinavir.

With respect to tipranavir, changes at another 11 protease positions were found to be the most important for causing resistance to the drug by an international research team (Scherer, et al. 6th European Resistance Workshop; Budapest, March 2008; abstract 94). The authors weighted their distinct impact and it came out that the changes affecting tipranavir susceptibility more are 74P, 47V, 58E, and 82L/T (see Table). Of note, these changes are rarely selected by other protease inhibitors.

At the latest Drug Resistance Workshop, held in Sitges, Spain in June 2008, international researchers (Hall, et al. Antivir Ther. 2008;13[Suppl 3]: abstract 124) reported that hypersusceptibility phenomena may be particularly important for tipranavir, while they are of less relevance for all other protease inhibitors. The non-peptidomimetic nature of tipranavir could explain this finding. Patients with viruses harboring one of the classical protease inhibitor resistance changes, such as 24I, 50L/V, 54L and 76V, demonstrated significantly improved virologic response to tipranavir-based regimens along with a decreased phenotypic resistance to the drug. In contrast, distinct degrees of phenotypic resistance were manifest for all other protease inhibitors, including darunavir.

Altogether, these results suggest that while the good responses to darunavir in salvage therapy are mainly explained by its high affinity binding to the HIV protease, the strong potency of tipranavir is mainly due to its distinct molecular design and non-peptidomimetic structure. It is noteworthy that while most resistance mutations are in the pathway of resistance to darunavir, very few are in the tipranavir resistance score. Thus, cross-resistance between these two potent protease inhibitors for salvage therapy should not be expected, and therefore they may be used sequentially, opening up opportunities for this subset of patients with very few therapeutic options.

Table. Mutations involved in resistance to second-generation protease inhibitors

	Darunavir	Tipranavir
More impact		
	50V	74P
	54L	47V
	76V	58E
	84V	82L/T
Less impact		
	32I	83D
	33F	54A/M/V
	47V	36I
	11L	43T
	54M	84V
	74P	10V
	89V	46L

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