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Review

Genotyping and NNRTI mutations: where do we go from here as HIV populations get older? A perspective

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As genotyping procedures have increasingly become more sensitive and complex, HIV scientists and physicians are finding new clinical approaches to treat compromised patient populations on non-nucleoside transcriptase inhibitor (NNRTI) classes of drugs. Further, as age demographics play a vital role in older populations affected with HIV, understanding phenotype/resistance panels for regimen changes is paramount.

Key words: HIV/AIDS, gerontology and geriatrics, micro biology.

INTRODUCTION

Each year at the HIV Resistance Conference, the issue of non-adherence or (non-compliance) and genotyping surfaces as it relates to HIV treatment regimens. In an effort to vigorously address this issue, resistance or phenotype testing has gained traction in recent years.
As genotyping procedures have increasingly become more sensitive and complex, HIV scientists and physicians are finding new clinical approaches to treat compromised patient populations on non-nucleoside transcriptase inhibitor (NNRTI) classes of drugs. Further, as age demographics play a vital role in older populations affected with HIV, understanding phenotype/resistance panels for regimen changes is paramount. Particularly, medical directors of skilled nursing facilities that have residents with HIV.

Ten percent of AIDS cases reported in the United States have been among individuals ages 50 and above (CDC, 1999). With highly active antiretroviral therapy (HAART) extending lives much beyond what was hoped for just 5 years ago, more individuals are living into their sixth decade and beyond. Simultaneously, changes in demographic patterns and social norms may be increasing the risk for HIV among people in their 50s, and 60s. The convergence of these factors warrants increased attention to the impact of HIV disease among older Americans (CDC, 2000).

As many of you may know, genotyping refers to the process of determining the genotype of an individual with a biological assay. Current methods of doing this include PCR, DNA sequencing, and hybridization to DNA chips or beads. The technology is intrinsic for test on father-/motherhood and in clinical research for the investigation of disease-associated genes. Further, the genotype is the specific genetic makeup (the specific genome) of an individual, in the form of DNA (Cohen et al., 2006). Together with the environmental variation that influences the individual, it codes for the phenotype of that individual. Non-hereditary mutations are not classically understood as representing the individuals' genotype. Hence, scientists and physicians sometimes talk for example about the (geno) type of a particular cancer, thus separating the disease from the diseased. While codons for different amino acids may change in a random mutation (changing the sequence coding a gene), this does not necessarily alter the phenotype (Cohen et al., 2006).

NNRTI's are a class of anti-HIV drugs. When one NNRTI is used in combination with other anti-HIV drugs – usually a total of 3 drugs – then this combination therapy can block the replication of HIV in a person's blood. NNRTI's, sometimes referred to as "Non-Nucleoside Analogues" – or "non-nukes" (Cohen et al., 2006) for short – prevent healthy T-cells in the body from becoming infected with HIV (AIDSMED). When HIV infects a cell in a person's body, it copies its own genetic code into the cell's DNA. In this way, the cell is then "programmed" to create new copies of HIV. HIV's genetic material is in the form of RNA. In order for it to infect T-cells, it must first convert its RNA into DNA. HIV's reverse transcriptase enzyme is needed to perform this process. NNRTIs attach themselves to reverse transcriptase and prevent the

the enzyme from converting RNA to DNA. In turn, HIV's genetic material cannot be incorporated into the healthy genetic material of the cell, and prevents the cell from producing new virus (AIDSMED).

NNRTI's such as Atripla™, Sustiva®, Viramune® and Resciptor® (brand names) have all been instrumental in the fight of attempting to eliminate the replication of HIV in healthy cells of a HIV patient (with combination therapy). The challenge for many clinicians is knowing when to switch treatment regimens, when failure of previous regimens is apparent. The consequences of clinical failure can be significant.

If clinical failure is evident, does the clinician opt for partial interruption or complete treatment interruption? There has been significant discussion in the infectious disease community concerning treatment interruption. Based on the results, the mean change in Viral RNA and the mean change in CD4 count are two indicators (AIDSMED) to consider in this decision (3TC Monotherapy vs. treatment interruption). Another issue in understanding resistance panels, determining the Continuous Phenotypic Susceptibility Score (cPSS) is crucial (Levin, 2003). Elements to consider in this equation: 1. activity of drug defined by relation to clinical cutoff, 2. maximum score. 3. minimum score, 4. mor drugs where final cutoff is < upper cutoff, get partial score (0 to 1), (AIDSMED; CDC, 2000). After the cPSS has been determined, the clinician can ascertain how many new drugs to add to the patient's regimen.

Those in the infectious disease and geriatrics communities will hear more of resistance testing in the 21st century, due to the dynamic and complex environment of drug resistance. Managing patients (particularly, older patients with HIV) will become even more challenging, as a result of an expanded menu of new classes of HIV drugs and as dynamic patterns of resistance increase in the older population.

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