Editorial

Resistance to Antiretroviral Therapy

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Survival of the fittest is the law of the nature! It was discovered by Sir Charles Darwin and explained with his theory of evolution.

Self survival and replication for the propagation of the race are the two basic goals of every living organism. Under the pressure of adverse circumstances, there is a slow genetic evolution which brings in the fitness to survive under adverse circumstances and the fittest organism is selected for further propagation.

Human Immuno Deficiency virus is no exception! An infected person has a very high viral replication rate with a turnover of HIV – approximately 10 million new viral particles are produced every day. Reverse transcription which lacks a proof reading mechanism, is a part of its replication process. As a result there is a constant production of new viral strains due to a very high mutation rate even in the absence of drug pressure.

Emergence of the drug resistance is a slow process. It may be instantaneous but usually may take several rounds of replication. Amongst the diversified strains, one variant with strong survival benefit is selected.

In the ART experienced patient HIV will continuously experience selective pressure to evolve resistance to the drugs. However even in drug naïve cases the resistant HIV is generally at a competitive disadvantage i.e. exhibits lower “fitness compared to wild type virus.” Resistant mutation often reduces the viral replicative capacity and it may also reduce its ability to infect CD4 T cells. These secondary effects are referred to as a “fitness cost” of resistance. A strong evolutionary pressure exists in vivo whereby drug sensitive (wild type) virus outcompetes drug resistant virus in the absence of drug pressure.

HIV’s capacity for latency is to be appreciated. Under the ART pressure, the viral load of the sensitive virus decreases and the resistant viral population dominates in the individual but with the interruption of the ART, the sensitive virus from reservoirs rapidly overgrows and become a new dominant quasi-species. However if the same individual restarts ART, latent resistant virus regains a competitive advantage and regains dominance. These issues are very pertinent for defining the frequency of HIV transmission.

Unfortunately, there is no ARV drug combination as yet which could completely stop the HIV replication. Therefore, our present goal of ART is to achieve maximum suppression of viral replication. The effective ART must result in undetectable (<50copies/mL) load at 16-24 weeks. The most common cause of therapeutic failure is a viral resistance as it indicates ongoing viral replication the in presence of the inhibitory drugs. During the antiretroviral therapy the virological failure appears first. Immunological failure becomes evident much later followed by the clinical failure. Therefore, viral load monitoring is essential to detect virological failure at the earliest so as to switch the therapy.

The understanding of the mechanism of the drug resistance has redefined the site of action of the drug and their metabolic pathways. It has helped in designing newer molecules.

The viral resistance is measured indirectly by genotypic assays and directly by phenotypic assays. For both the assays, viral load in a patient needs to be more than 1000 copies / mL. The ultra sensitive methods such as allele-specific real-time PCR or ultra-deep sequencing are being presently used as research tools in cases of viral load less than 1000 copies.

The phenotypic assays directly measure the drug susceptibility. It also considers the complexity of resistance pattern and the presence of re-sensitizing mutations. However they are very expensive, and time consuming.

The genotypic assays reveal the mutation which is a change in the nucleotide sequence of a codon. Lethal mutations cause a defective protein structure leading to a stop of a viral replicative cycle. It can be performed quickly, used widely. It also identifies the clades of HIV. Interpretation of the results are data based eg Stanford, aNRS, IAS etc. So far the data is available about HIV subtype B. Non B subtype data is scanty and needs to be studied further. Genotypic assays have revealed the cross resistance to the other drugs in the same class. Accumulation of thymidine analog mutations (TAMs) with the use of NdRTI drugs have shown reduced sensitivity / resistance to Tenofovir, the NRTI.

Viral load monitoring and drug resistance assays are necessary to guide the clinicians for proper selection of ARVs.

With rising incidence of ARV resistance, there is evidence of increasing number of transmitted drug resistance in newly infected cases.

In 2007 an International research group agreed upon the criteria defining mutations indicative of transmitted resistance. The prevalence of primary resistance varies from country to country. CAPTORE cohort revealed 17% had mutations that added up to triple class resistance.

The 2007 DHHS antiretroviral guidelines recommend ARV drug resistance testing in all the newly infected drug naïve cases.

Factors like lack of therapy counseling, non – adherence, substandard drugs, suboptimal therapy, irregular supply of drugs, risk behavior of the patient contribute to the development of drug resistance. But in Govt. driven public health programme most of these factors are minimized with uniform protocols. However the quality of the implementation may be compromised.

Virological failure must be the indication to switch the therapy. Immunological failure followed by the clinical failure may be very late indicators to change the therapy. In fact there is a growing evidence that the late switch to second line therapy may result in to an effective monotherapy.

Therefore, viral load monitoring even in the resource limited countries has no substitute.

References

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