



Challenges of Antiretroviral Therapy

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The availability of potent antiretroviral drugs and their use in 3 or more combination regimens- Highly Active Antiretroviral Therapy (HAART)- has led to a dramatic decline in the morbidity and mortality associated with Human Immunodeficiency Virus (HIV) infection. Despite these tremendous and impressive achievements, the treatment of HIV faces significant challenges in the years to come.

It has become clear that antiretroviral therapy, at least in its current form, will not be able to eradicate HIV infection. Therefore, the realistic expectations of antiretroviral therapy currently are that HIV-infected patients will have to be treated with antiretroviral drugs life long. In spite of the successes of antiretroviral therapy noted above, the long-term efficacy of these drugs has not been established. Additionally, the optimal way to use antiretrovirals - when to initiate therapy, when to switch, utility of resistance testing, strategies of treatment (continuous versus interrupted), role of adjunctive immune-based therapies, sequencing of agents and regimens- has not been satisfactorily defined.

Currently there are seventeen Food and Drug Administration (FDA) approved individual antiretroviral drugs and two additional coformulated products categorized in four classes of drugs. While the number of antiretroviral drugs available make it appear that there is a potential for a vast number of likely drug combinations, in reality, it is difficult to construct even three regimens that are reliably effective when given sequentially. This is primarily because of significant cross-resistance among agents of the same class. There is a continued need for the development of potent antiretroviral drugs that target various points in the HIV life cycle and have the additional properties of low pill burden, low potential for short-term and long-term toxicities, and favorable pharmacokinetics as well as drug-drug and drug-food interaction profile.

There is now an increased appreciation and recognition of the importance of patient adherence to prescribed antiretroviral regimens to ensure successful virologic suppression and clinical outcome. Several studies have now documented that near perfect adherence to prescribed antiretrovirals is necessary to achieve and sustain viral suppression. Some of the strategies adapted to assist patients in adhering to treatment regimens include changes in clinical practice and engagement of a multidisciplinary team to educate, counsel, and motivate patients as well as monitor, identify, and address psychosocial issues and drug-related toxicities before they result in nonadherence. The availability of drugs and regimens that are simple and with a favorable short-term and long-term toxicity profile will considerably aid this effort.

As HIV-infected individuals live longer and are exposed to various drug combinations over longer time periods, the long-term safety of antiretroviral therapy becomes an increasingly important concern. New side effects have become manifest with the continued wide spread use of antiretroviral drugs. Metabolic complications of these drugs have included hyperglycemia, insulin resistance, frank diabetes mellitus as well as abnormalities of lipid metabolism and lipid deposition (cutaneous fat wasting, visceral obesity, cervical fat pad). The biochemical and physiological basis of these metabolic complications are yet to be elucidated and it is not known if these metabolic complications will translate into increased risk of vascular or other disease.

Finally, antiretroviral therapy is not available to the overwhelming majority of HIV-infected people. Of the 42 million people that are infected with HIV worldwide, approximately 95% live in resource-limited settings. There has been increased awareness of the need to introduce, implement, and sustain antiretroviral therapy in these countries. While the obstacles to this effort are formidable, they are not insolvable.