



Challenges in the Use of Antiretrovirals in Resource Limited Settings

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Highly Active Antiretroviral Therapy (HAART) has dramatically altered the course of HIV infection, mortality rates have plummeted and many infected patients able to access this therapy are leading reasonably normal productive lives. Unfortunately the drugs have been too expensive and inaccessible to effectively treat the vast majority of the 60 million persons infected worldwide. In addition, the drug regimens have been complicated to administer with large pill burdens, some must be given with and others without food, significant drug-drug interactions especially with tuberculosis therapy and if adherence to regimens drops below 90% of dosages, therapeutic failures rise and drug resistant viruses emerge. Protocols for management of patients have developed that require frequent use of expensive laboratory tests including quantitative measures of viral load, CD4 cell counts and more recently use of genotype and phenotype resistance testing. These complexities and expenses have created a daunting challenge for introducing and sustaining HAART in resource-limited areas such as sub-Saharan Africa.

Creative approaches are needed and since the “western approach” is impractical in this setting it must be challenged and new paradigms developed. The following challenges need to be addressed:

- Build Infrastructure for delivery of enhanced HIV/AIDS care and prevention by training health care providers (physicians, medical officers, nurses, laboratory technicians & pharmacists) and developing delivery systems by which drugs and care can be provided. Systems must also be developed to protect these providers from occupationally acquired infections (HIV, HBV, HCV and TB).
- Maximize cost reductions from the pharmaceutical companies and then subsidize drugs purchases with western resources (Global Fund, The US Presidents initiative, etc); drug costs have dropped dramatically and with generic and patented drugs now are in the \$1/day range but still out of reach for the vast majority who could benefit.
- Develop and validate clinical and simple laboratory criteria to replace expensive laboratory tests; are viral loads and CD4 counts really necessary to make decisions about starting or changing therapy or could clinical and simple laboratory tests such as weight, symptoms (appetite), signs (thrush) and total lymphocyte counts be as effective? The current accepted standards are unique in the field of infectious diseases; others may be just as good!
- Challenge current dosing schedules; lower doses of some ARVs may be as effective, less toxic and less expensive.
- Determine geographic specific genetic and environmental factors that might influence disease and therapy: drug absorption (parasites, diet {matoke}, etc); drug metabolism (are there unique characteristics in P450 activities or other metabolic pathways in the African populations?); drug interactions (many will be on TB rx); co-infections; TB, malaria, intestinal parasites, etc; climate (indinavir stones are more common in hot climates, need for drug refrigeration, etc); Influence of different HIV clades unique to area; pathogenesis, infec-

tiousness?

- Determine factors that influence adherence in this environment; recent data suggests that Africans may take drugs better than Americans.
- Unstructured treatment interruptions of HAART will be common if patients are required to pay for drugs; what will be the consequence? Recent data suggests that it may still be much more effective than no HAART, maybe ok if all drugs started and stopped together but what about those with long t_{1/2} lives (Nevirapine), will resistance emerge?
- Single dose Nevirapine to mother and newborn are currently recommended to prevent mother to child transmission of HIV in resource limited areas and result in 50% reduction in transmission however significant numbers of infants still get infected during breast feeding. New strategies are needed (mothers may need ARVs during breast feeding).
- Will the introduction of ARVs into Africa be perceived that a cure is now available and undo the gains made in risk reduction and in actual decrease in infection incidence (in Uganda) as happened in some cities in the US? A campaign must be launched to send the correct message to the susceptible population.

These challenges are formidable but solutions are attainable. A commitment from the academic community in the developed world to help is critical!