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FACULTY OF MEDICINE
MAKERERE UNIVERSITY

ATIC newsletter

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INFECTIOUS DISEASES INSTITUTE

Quarterly Newsletter of the AIDS treatment information centre, Infectious Diseases Institute, Makerere University, Kampala

SECOND LINE SURPRISES

Dr. Charles Steinberg

Consultant, Training Department, Infectious Diseases Institute.

Now that our patients (referred to as "friends" at IDI) have had years on ART, it is predictable that some will find their regimen failing and need second line therapy.

The decision to switch a patient from 1st to 2nd line therapy is a serious decision that requires careful consideration. At IDI, there is great support in this decision - making process from the "The Switch Meeting."

The switch meeting is held every Tuesday morning between 8 – 9am,.

Clinicians from within IDI, visiting clinicians from other hospitals /countries and counselors gather and usually 2-3 cases, thought to be regimen failure, are presented and discussed.

As a group a way forward is determined. Decisions that may be taken include;

- *enhanced adherence counseling while continuing first-line then later repeating CD4*
- *checking a viral load if the patient has not had a viral load done before*
- *switching to second-line*
- *referring to a study.*

Sometimes compromises like a "holding regimen" are chosen to buy time. "A holding regimen would be described as a regimen that a patient, whose 1st line regimen has failed them , would be kept on if there was a delay of switching to a 2nd line regimen. the delay could be due to challenges in drug logistics, time needed to sort out adherence issues etc .

In principle, a holding regimen should continue to confer some advantages of drug therapy without leading to additional mutations that could cause further resistance . One example of such a regimen would be a 3TC only regimen."

Usually the decision the group comes to, with input from medical and psychosocial caregivers, is better than any one individual could do. Teamwork works and that is not a surprise.

When second-line is started, we are all familiar with the need for more counseling to cover the new drugs, how they are taken, their potential side effects, and in particular to look for any adherence issues that came up on first-line that need to be corrected before second-line can be initiated. IDI is currently referring some patients into a second-line study (The EARNEST Trial) or using Truvada (Tenofovir plus FTC) and Alluvia (Ritonovir boosted Lopinovir). This regimen has many advantages and is well tolerated and usually very effective. After a patient begins this we usually see them improve clinically and immunologically.

There are, however some potential surprises along the way, and if you the clinician are thinking about these, you will be prepared instead of surprised. Ask yourself before you read on, "What surprises might I be vigilant about in this patient and how should I be prepared?" Here are the surprises I think about. We'd welcome letters about others you have seen.

New Toxicities

SURPRISE: My patient's legs are swollen.

While Tenofovir itself probably does not cause much primary kidney disease, it has the potential to make underlying kidney disease progress. Ideally we want to check a serum crea-

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INSIDE STORIES

EDITORIAL

Dear Reader,

It has been about six years since the Ministry of Health rolled out antiretroviral therapy (ART). Since then, the quality and span of life of people living with HIV (PLWH) has improved tremendously. Some couples living with HIV have been able to have healthy children and also been able to see their other children grow into adults.

Overtime, due to several situations, some people experience treatment failure. Treatment failure is the situation where the ARVs can not control the viral infection. The factors that increase the risk of treatment failure include:

- *decreased susceptibility of the HIV virus to the drugs due to mutations within the virus .*
- *poor adherence to treatment*
- *poorer health before starting treatment.*
- *alcohol abuse leading to poor treatment adherence*

When a patient fails on one regimen for one reason or the other, the clinicians will switch the patient to another regimen. This decision to switch from one regimen to another should not be taken lightly. This involves understanding why treatment failed; evaluation of treatment history, medication side effects and physical condition of patient. After thorough consideration, then the patient is switched.

In this Issue we bring you articles on switching from one regimen to another. We hope they are helpful to you as you continue to manage your patients.

Allen Mukwana/Editor

SECOND LINE SURPRISES *continued from Pg 1*

tinine and calculate the creatinine clearance for any patient going on Tenofovir. Also a urine dip stick for protein is a good screen. If there is significant decrease in the creatinine clearance, we may need to adjust the dose of Truvada or choose other agents not affected by renal function.
So by initially checking a patient's renal function, you will adjust doses as needed, monitor closely and not be surprised by your patient going into renal failure. The incidence of HIV Associated Nephropathy (HIVAN) in our setting is still unknown. *Beep ATIC for more information.*

SURPRISE: My patient is getting a huge belly.
All protease inhibitors are related to the form of lipodystrophy characterized by the central accumulation of fat. Initially called "Crix-Belly" because of its association with Crixivan (Indinavir), this can occur with any protease inhibitor including Aluvia. This fat is intra-abdominal, deep to the muscular layer, and sometimes in the neck and the dorsal fat pad. It can make the patient very uncomfortable. Aluvia is not the worst culprit, but we can be watchful for early signs of this and encourage healthy diet and exercise.

Drug Interactions

SURPRISE: A drug my patient takes from his other doctors is now making him sick. We must remember that the ritonavir in Alluvia (or Kaletra) is a potent blocker of the cytochrome CYP 3A pathway, and drugs from midazolam to Viagra can build to toxic levels. Beep ATIC for more information on all other drugs your patient is taking. Drugs in common use in our setting include ketoconazole, rifampicin, some of the statins and Coartem. These and many more can have significant interactions. And while not well understood, ritonavir has occasionally worsened the renal toxicity of tenofovir. The very best practice is to ask our patients to bring in everything they are taking every visit. The surprises we find in those bags… herbal products, anti-psychotics, drugs for this and that we didn't know about. So don't let your patient surprise you, routinely ask to see what they are taking.

Immune reconstitution inflammatory syndrome (IRIS)

SURPRISE: My patient is getting worse. New fevers, huge swellings, cough, and headache - what's happening?
One thing we don't often think of, and thus it can surprise us, is an IRIS reaction after starting second-line ARVs. The set up is the same as the usual IRIS we see when starting first-line. There is rapid immune reconstitution from severe immunodeficiency and the healthier immune system can now put up a fight against living or dead organisms. And that fight spells symptoms. During the time the patient was on the failing first line regimen, an O.I. may have developed either apparent and treated or occult and undiagnosed. So we need to learn to expect this and not be surprised.

Conclusion: Overall the real surprise has been how great adherence has been in most Resource Limited Settings, and how long so many of our patient's virus remains suppressed on first-line ARVs. There will, however, be a growing need for second-line regimens. I hope for our next surprise to be a few more agents so we will have even a third line to turn to if our second-line regimen fails.

RIGHTS HERE, RIGHT NOW

Dr. Ceppie Merry
HIV Physician and Pharmacologist
Trinity College Dublin and The Infectoius Diseases Institute- Mulago.

The 18th International AIDS Conference was held in July in Vienna, Austria, where the global community had the chance to examine the continuing response to the HIV /AIDS pandemic. The theme of the conference was Rights Here, Right Now.

On the 21st and 22nd of July 2010, ATIC, IDI staff and the wider community were able to attend an off-site hub of the 18th International AIDS conference. The hub relayed downloaded material from the conference highlighting clinical and prevention aspects of the meeting in Vienna. This was held in the Davis Lecture Theatre at the College of Health Sciences, Makerere University

The materials presented varied from epidemiology and human rights to paediatric adherence to the keynote address from former US President Bill Clinton.
There was a panel of local moderators who provided important support to help make the materials more relevant in a Ugandan and African context, as well as to stimulate discussion amongst those present.

During the conference, several sessions underscored the cost-effectiveness of treating early versus treating later, when costly opportunistic infections begin to emerge. During a "When to Start" panel, Dr. Peter Mugyenyi, Director and Founder of the Joint Clinical Research Centre in Kampala, Uganda, said the cost of treating an opportunistic infection like cytomegalovirus for one month is equal to the cost of providing HIV treatment for three years in Uganda.,
Another presenter from Uganda, Mary Munyagwa reported on a cohort study investigating the impact of HIV on paediatric mortality in rural South Western Uganda. This study which followed HIV infected and uninfected children for a period of 7 years showed that the mortality rate was over 6 times higher in HIV-positive children not yet on ART than in HIV negative children and that among HIV positive children, mortality was highest among those aged less than 2 years. This is in line with the previous finding that perinatal HIV transmission is associated with rapid disease progression.

The study also found that introduction of ART resulted in a small reduction in mortality which was not statistically significant. The lack of a significant association between ART and decreased mortality may be because of delays in starting ART

She concluded that decreasing child mortality due to HIV in rural Africa requires intensified efforts to prevent mother- to- child transmission of HIV and to ensure early HIV diagnosis and treatment.

The discussion following the presentations was lively, relevant and was guided by IDI, JCRC and Makerere clinical and academic staff. Attendance was impressive both days, showing the great interest in current developments in HIV/AIDS research and care from ATIC, IDI and the surrounding institutions.

One of the plenary speakers at the International AIDS Society Conference was the former President of the USA, Bill Clinton. He acknowledged the many successes in the field of HIV/AIDS and expressed delight that there are now 5.2 million people worldwide including 300,000 children on antiretroviral (ARV) drugs. He was proud that his organisation, the Clinton Health Access Initiative had helped reduce the cost of ARVs especially for children where the costs have dropped from USD 600 to 60 per year.
Clinton quoted Churchill who once said, "This is not the end, and not even the beginning of the end but just that this is merely the end of the beginning".
He commented that the successes so far should not be an excuse to walk away from human rights and HIV/AIDS but to run towards those rights now that we have a positive proof of concept.
Clinton made an eloquent case for the need to move from a 'make it up as you go along' emergency response that we have had thus far to a sustained, co-ordinated and streamlined approach as we move forward so that we can maximise our impact in times of limited resources.
He said that one of the challenges to the scale up of ARVs in Africa was the lack of trained healthcare workers. This was illustrated by quoting varying percentages of Africa's situation i.e. Africa has 10% of the world's population, 25% of the world's health care burden and just 3% of the workforce. This necessitates new approaches to health care delivery whereby we can increase the number of

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EARNEST TRIAL

EARNEST stands for Europe-Africa Research Network for Evaluation of Second line Therapy

Dr. Ivan. Kiggundu Mambule, MBchB

It is an international open label, multi-center, randomized clinical trial and is the first, second line trial of its magnitude in Sub-Saharan. Africa.
EARNEST is coordinated by the Medical Research Council (MRC-UK) and is enrolling in three African countries, namely, Uganda, Zimbabwe and Malawi.

The active centers of enrollment include are

- Infectious Diseases Institute, Joint Clinical Research Center, and Nsambya Hospital in Uganda;
- University of Zimbabwe Clinical Research Centre (UZCRC) in Zimbabwe and
- Queen Elizabeth Central Hospital in Blantyre, Malawi.

Our patients are randomized to one of three arms each with a known second line therapy. Our main objective as a study team is to recruit 1,200 patients who are failing on 1st line and follow them up on 2nd line for a duration of three years.

So why EARNEST?

A combination of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and 1 Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) is the most common choice of 1st line HAART in the world and such a combination has been shown to be effective in preventing or reversing the decline in immune function. It reduces the risk of opportunistic infections and as a result there is reduction in morbidity and mortality from HIV.

However, clinical trial data indicates that 20-30% of patients on 1st line HAART fail to achieve sustained viral load suppression (less than 50 copies/ml), even after prolonged (144 weeks) treatment with the 2 NRTIs + 1NNRTI regimen.

In Africa, there's limited data on failure rates but you can be sure that with infrequent or absent viral load monitoring and therefore huge dependence on immunological (CD4) or clinical parameters for treatment monitoring, virologic failure is detected late. Consequently, there is a higher probability of patients ending up with extensive resistance mutations.

In addition, in resource limited settings, we do not routinely carry out resistance testing and the availability of 2nd line drugs is limited. This means that we lack the capability to individualise 2nd line therapy.

Second line therapy in most guidelines is recommended to contain a boosted Protease Inhibitor (PI) and 2 NRTIs. Although this regimen is usually very effective, it has some weaknesses.
A case in point is one phase II trial comparing this 2nd line to the use of 2NRTIs plus a new NNRTI (entravirine) in the management of 116 adults who were failing on first line NNRTI based therapy. Although this trial was terminated early due to superiority of the boosted PI arm. It showed that 25% of patients on the bPI arm failed to achieve active VL suppression by week 24. With the knowledge that we tend to diagnose failure late and therefore, a possibility of extensive mutations to the NRTI class, could there be a possibility that recycling the NRTI class just might not be helpful? Or that it might even increase toxicity and the cost burden of second line? It is not known for sure, because no study to date has answered this question in a resource limited setting basing on a large number of patients.
A question is asked then: How would you best determine the most effective second line option?

The following options could be considered;

Option A: Boosted PI (bPI) + Entravirine:
Entravirine is a new NNRTI, which has been shown to have activity even after failure on nevirapine and efavirenz. However, as already mentioned, we tend to switch patients late and therefore, the activity of this drug can be compromised by emergence of the Y181C a mutation common with treatment failure on nevirapine.

Option B: bPI + Maraviroc:
Maraviroc is a CCR5 blocker.
However, we know that most patients with advanced HIV have a virus which predominantly prefers using the CXCR4 co-receptor and therefore, maraviroc might not be active on failing patients. Tropism testing would then be important. However tropism testing is very expensive and unavailable in most of Sub Saharan Africa.

Option C: bPI + Raltegravir
Raltegravir belongs to a new class of ARV drugs called Integrase Inhibitors.
A combination of a boosted PI and raltegravir would be an option on two fronts;

- It has shown to achieve better viral load suppression than the conventional Aluvvia + 2NRTI combination. The PROGRESS study which compared Aluvia + 2NRTIs with Aluvia + Raltegravir in naïve patients showed significantly higher proportion of VL sup pression at eight weeks for the Aluvia + Raltegravir arm.
- Raltegravir also has no cross-resistance with 1st line drugs and therefore, to use it as 2nd line no resistance testing is needed.

Option D: bPI Monotherapy:
Two studies, OK O4, and KALMO have compared LPV/r monotherapy with standard HAART.
In these studies, patients who were on triple ART and were virologically suppressed and randomly assigned them either to continue HAART or to start on bPI monotherapy.

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RIGHTS HERE, RIGHT NOW

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healthcare workers who can do good work at a lower cost in a wider geographic area than the conventional medical model. Such an approach includes, but is not limited to task-shifting.

Health workers, listening to presentations at the Davis lecture theatre, Mulago

He thanked Irish Aid for supporting CD4 technology being used in Mozambique. He emphasized the need for African countries to recognise and utilise their own resources to fund health especially in countries with new found wealth.

He also reminded us that HIV has had the most rapid rate of investment applied to any public health problem in human history (6 to 16 billion USD over the last four years) and that now that we have entered an era of uncertain funding that we are being misled by what he called false choices such as whether to invest in health systems or maternal health. He was sceptical about the 'either, or ' decisions. Clinton argues that this is a false choice and our real choice is not what to make happen but how to make it all happen.

He said the interconnectedness of life and how investing in any sector of health impacted on all other sectors and hence it was a false choice between health systems and maternal health as investment in one without the other would be futile. Investment in health systems without investment in drugs for prevention of mother-to-child transmission could result in a situation where people sit in nice offices and just say no to women! He further supported his argument by reminding us that investment in Global Health and HIV/AIDS has helped to solve more than one problem. For example investment in maternal health has reduced mother-to-child transmission of HIV and investment in HIV/AIDS has helped reduce maternal mortality.

Clinton divulged his dreams for the future, which includes climbing Kilimanjaro before the snow melts, running a marathon, as well as living long enough to see the birth of his grandchildren. He added his wish to "live to know that all the grandchildren of the world will have the chance in the not too distant future to live their own dreams and not die before their time."

He said that the only chance for humanity is that we tap into the positive within us.

CHOOSING A SECOND LINE ART REGIMEN FOR CHILDREN

Mutabaazi William
Senior Pharmacist-NEP
Baylor – Uganda

When we start patients on antiretroviral therapy, we tell them that treatment will be life-long. We tell them that they should take their drugs without missing doses (or else their treatment will fail to work) and that they should choose dosing times that are agreeable with their schedules.

We anticipate the difficulties our patients will have in adhering to their medicines and so we offer them support in form of adherence counseling, choosing of treatment buddies, provision of pill boxes and other such things.

These interventions work well when dealing with adult patients. However, with children as our patients, we encounter these difficulties on a whole new level.

Adherence to an antiretroviral regimen which is one of the most important factors that leads to success of antiretroviral therapy (ART) is much harder to ensure in children than it is in adults.

This is because ensuring adherence in children is often an interplay between the child the caretaker and the child's environment

- Most children depend on someone older for the success of their treatment. The caretaker will often decide when the child will take their medicines and how much they take. The caretaker may forget to give the medications or may forget to collect the medicines from the health facility
- Children, especially those below the age of 5years may not properly appreciate the importance of taking their medicines everyday especially if they have not been disclosed to, so if they get drug related complications or if the drug has unpalatable preparations, they may refuse or fail to take it.
- The child's environment can play a big part in aiding or hindering their adherence to an antiretroviral regimen., intermittent drug supplies in health facilities , inappropriate formulations of drugs e.g. unscored tablets that have to

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EARNEST TRIAL *continued from Pg 4*

The results showed bPI monotherapy can maintain virologic suppression.

On the other hand, the MONARK and MO3-613 trials which enrolled naïve patients and randomized them to either bPI Monotherapy or to standard HAART, showed that the monotherapy arm had a high proportion of patients with low viraemia and eventual analysis showed inferiority of the bPI monotherapy arm.

Taken together, we can infer that mono PI is a viable option for second line only after achieving virologic suppression.

So what is the rationale for carrying out this study?
Following a massive rollout of ART in Africa, we expect that over the coming few years an increasing number of patients on 1st line HAART will be developing treatment failure and will require 2nd line therapy. As a consequence, there is urgent need to develop evidence for 2nd line therapy in Sub Saharan Africa and in other low income countries.

Objectives of the trial

The trial aims at determining whether patients failing on a 1st line NRTI and NNRTI regimen;

1) The use of a boosted PI plus Raltegravir (integrase inhibitor) is superior to standard of care (bPI + NRTIs)
2) The use of bPI monotherapy in non-inferior to standard of care

Trial design / intervention
A total of 1,200 patients will be randomized to 1 of 3 arms
Arm A: Boosted PI +NRTIs (standard of care)
Arm B: Boosted PI + Raltegravir (taken continuously for 144 weeks)
Arm C: Boosted PI alone (After an initial 12 week induction phase with Raltegravir)

Inclusion Criteria

1) Previously documented HIV infection
2) 12 years and over
3) Taken 2 NRTI and 1NNRTI based regimen continuously for 12 months and over
4) Naïve to protease inhibitor therapy
5) HIV treatment failure

What is treatment failure?
It is divided into three forms/categories used independently or in combination.

Clinical failure:

New or recurrent WHO Stage IV event occurring after at least 12 months on ART;
Immunologic failure:

- A fall in CD4 counts of more than 50% on two or more occasions
  from the on-treatment peak value or
- A return to, or below, the pre-therapy baseline or
- Persistent CD4 levels below 100 cells/mm3.

Virologic failure:
No uniformly accepted definitions, but persistent detectable viraemia (over 50 copies/ml) is indicative of incomplete viral suppression. For purposes of this study, we consider this a failure if the VL is greater than 10,000. This is because values greater than 10,000 copies/ml have been associated with subsequent clinical progression.

Exclusion Criteria

1) Contraindications to boosted PI and/or Raltegravir
2) Known Hepatitis B
3) Pregnant women

Duration

Each of our patients will be followed up for a total of 144 weeks and after this, the patient will transfer back to the national ART program for follow up.
At the moment we have enrolled over 60 patients at IDI and the study as a whole is about 20% enrolled. Therefore, a large number of patients is still required to give the study the much needed power.
Patients who are suspect to be failing on 1st line ART can be referred to any of the centers listed below:

SITE	CONTACT TELEPHONE	EMAIL
Uganda		
IDI	+256772594411,	
	+256 772 661899	imambule@idi.co.ug
JCRC Kampala	+2564142170283	ckityo@jcrc.co.ug
JCRC Mbarara	+2564142170283	ckityo@jcrc.co.ug
JCRC Fort portal	+256 773291297	marykiconco@gmail.com
JCRC Mbale	+2564142170283	ckityo@jcrc.co.ug
Nsambya Hospital	+256772435383	Mbayo2001@yahoo.com
Malawi		
Queen Elizabeth Central Hospital Blantyre, Malawi	+265999330307	janemallewa@yahoo.com
Zimbabwe		
University of Zimbabwe Clinical Research Centre, Harare , Zimbabwe	+2634705986	reid@uzcrc.co.zw

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be broken may act as a hindrance to regimen success.

The combination of inadequate dosing changes during growth and development, incomplete viral suppression, adherence difficulties, and lack of access to potent infant and pediatric ARV formulations can all contribute to treatment failure and ARV drug resistance. It has been found that treatment failure is twice as likely to occur in children as it is in adults . In a study done by Kamya et al in Kampala, 26% of all children vs 14% of adults were likely to experience virologic failure at 12 months of treatment

Treatment failure is suspected when a child has increasing episodes of opportunistic infections, reducing CD4 % /CD4counts and detectable/increasing viral loads overtime. Treatment failure is defined by WHO as either clinical, immunological or virological failure

- Clinical failure is defined as the appearance or reappearance of WHO clinical stage 3 or stage 4 events after at least 24 weeks on ART in a treatment-adherent child.
- Immunological failure is defined as developing or return ing to the following age-related immunological thresholds after at least 24 weeks on ART, in a treatment-adherent child:
  CD4 count of <200 cells/mm3
  or %CD4+ <10 for a child ≥2 years to <5 years of age
  CD4 count of <100 cells/mm3
  for a child 5 years of age or older.
- Virological failure is recognized as a persistent VL above 5 000 RNA copies/ml, after at least 24 weeks on ART in a treatment-adherent child.

The current Ministry of Health guidelines state that all HIV positive children should be clinically staged and receive a CD4 test where possible to determine eligibility for ART. However, exception is made for children under 2 years of age who should be initiated on ART immediately irrespective of clinical or immunological status. This differs from the 2006 recommendation that suggested only children under 1 year of age should be initiated on ART irrespective of clinical or immunological status.

With the increasing campaigns for earlier treatment of HIV positive children the numbers of those accessing ART treatment will rise daily..

Baylor College of Medicine Children's Foundation-Uganda (Baylor-Uganda) currently supports the largest number of children infected and affected with HIV in Uganda. At the Baylor College of Medicine Bristol Myers Squibb Children's Clinical Centre of Excellence at Mulago Hospital (the headquarters), over 3000 children are receiving highly active antiretroviral therapy (HAART) with an average of 10-15 children initiated on HAART every week.

At Baylor-Uganda, 2.4% of the children on treatment fail on first line regimens and are switched to second line regimens annually and currently, 8% of the children on ART are on second line treatment plan.

Earlier initiation on ART means that treatment failure and drug resistance will occur earlier in childhood. This calls for the urgent development of evidence-based second-line therapy and salvage strategies. Ideally second line and salvage treatment plans should have at least three fully active ARVs selected on the basis of resistance testing. In the absence of resistance testing, second line drugs should be selected based on knowledge of resistance patterns of drugs in the patients' previous regimen.

Second line regimens should therefore be well thought out. It is preferred that the switch from first line ARVs is made through a consensus by various medical practitioners considering the following:-

1. First line regimens used
2. Availability and sustainability of second line options selected
3. Sex, age, of the patient.
4. Other underlying disease conditions
5. Psychosocial support from caretakers
6. Suitability of available second line formulations
7. Pill burdens
8. Drug interactions & other concurrent medication

The World Health Organization and the Ugandan Ministry of Health take the above factors into consideration when developing guidelines.

According to the new Uganda Ministry of Health Guidelines, the recommended second line regimens in children based on their first line regimens are:

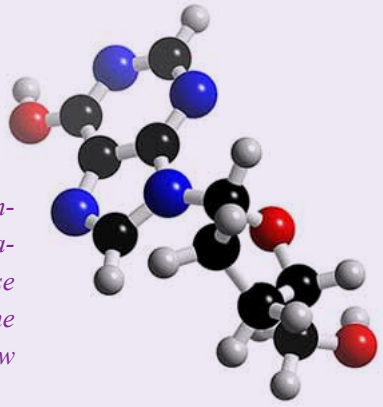
ART Regimens for Children		
	1st Line Therapy	2nd Line Therapy
Preferred	AZT + 3TC + (NVP or EFV)	ABC + 3TC + LPV/r
1st Alternative	ABC + 3TC + (NVP or EFV)	AZT + 3TC + LPV/r
2nd Alternative	d4T + 3TC + (NVP or EFV) (only < 5 yrs old)	ABC + 3TC + LPV/r
Exceptions to Standard Treatment Regimens		
1) If child was exposed to NVP during PMTCT, substitute NVP with LPV/r in 1st line (if LPV/r not available, use NVP)		
2) Don't use EFV in children less than 3 years, under 13 kgs, or in 1st trimester of pregnancy		
3) If child is anemic (Hb <7.5 g/dl)… use ABC (or D4T) instead of AZT		

Please note: TDF is not approved for children under 12 years.

For advise on Paediatric ART Dosing, please consult the MoH Chart (pull out) that is part of this newsletter.

DIDANOSINE

Monica Amuha Grace
B Pharm, MPS



Introduction

In this issue, our drug profile is on didanosine (Videx and Videx EC), a nucleoside reverse transcriptase inhibitor used in the treatment of HIV infection in adults, adolescents and pediatric patients. Didanosine inhibits the DNA synthesis of HIV by competitively inhibiting the enzyme reverse transcriptase and incorporating into the viral DNA thus halting replication of the virus. didanosine was historically used in combination with other antiretroviral drugs as first line regimen but is now reserved for second line therapy due to its toxicity profile and difficulties with administration.

In second line therapy ddI is used in combination with another nucleoside reverse transcriptase inhibitor (NRTI) either AZT or ABC and a Protease Inhibitor.

ddI is no longer used in combination with stavudine (d4T) nor tenofovir (TDF) because:

- Concurrent use with d4T results in additive toxicity and increases the risk of side effects such as lactic acidosis, pancreatitis and peripheral neuropathy.
- Concurrent use with TDF increases ddI plasma levels by 40 to 60%. This results in increased ddI toxicity. However lowering the dose of ddI to cater for this interaction has been associated with excessive virological failure especially when TDF/ddI are combined with an non nucleoside reverse transcriptase inhibitor (NNRTI).
- Paradoxical reductions or lack of increase in CD4+ cell counts (even in subjects with undetectable viral loads) have been reported in patients receiving TDF/ddI combinations. These reductions are seen most often after more than 6 months of treatment with a TDF/ddI-based regimen and when standard dose ddI (400 mg) was co-administered with TDF. These CD4+ T-cell declines have not been reported in patients receiving any other antiretroviral regimen, including those in which either TDF or ddI were part of the NRTI backbone.

Available formulations

Didanosine is available in both tablet, capsule and powder formulations;

Enteric coated capsules: 125, 200, 250, and 400 mg

Buffered chewable or dispersible tablets: 25, 50, 100, 150 and 200 mg

Buffered powder: 100, and 250 mg

Directions for Use

Because ddI absorption is reduced in the presence of food, it should be administered on an empty stomach (at least 30 minutes before or 2 hours after a meal)

The following table defines the administration schedule based on age and weight;

AGE	DAILY DOSE	COMMENTS
< 3 months	50mg/m²*/dose twice daily	**Oral solution from pediatric power 10mg/ml should be kept refrigerated
3 months - < 13 years	90-120mg/m²/dose twice daily	Chewable tablets are not to be swallowed whole but can be crushed or dispersed in clean drinking water or clear juice
Adolescents and adults: < 60kg	125mg twice daily or 250mg once daily	
< 60 kg	200 mg twice daily or 400mg once daily	

* **Body surface area (m^2)** = $\sqrt{\frac{ht(cm) \times wt(kg)}{3600}}$

**** In areas where access to refrigeration is restricted, the solution should be kept in its original container and tightly closed, wrapped in a polythene and kept in a pot of water. The pot may be placed in a basin of sand with water. However, Didanosine chewable tablets may be used instead of the oral solution.**

Special Considerations

Renal and Hepatic Impairment

Renal impairment: The following dose adjustments are recommended:

Creatinine Clearance (ml/min)	Patient Weight	
	> 60 kg Total Daily Dose	< 60 kg Total Daily Dose
> 60	400 mg	250 mg
30 – 59	200 mg	125 mg
10 – 29	125 mg	125 mg
< 10	125 mg	75 mg

Hepatic impairment: standard dose should be given however these patients should be monitored closely for evidence of toxicity.

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GENERAL ASPECTS OF RESISTANCE TO ANTIRETROVIRAL THERAPY.

Hakim Sendagire MBChB, MSc, PhD

Several categories of medicines, called antiretrovirals (ARVs), that can slow the progression of the disease process among individuals infected with HIV/AIDS, were discovered about 20 years ago but were not widely used in many parts of Africa and in Uganda in particular until about only 6 years ago. This delay can be attributed to several reasons; first is the cost of the drugs. Initially, these drugs were very expensive and unaffordable for most people in Africa. Secondly and of particular interest to this article was the fear of resistance.

The international community was apprehensive that availing drugs to Africa where there is limited infrastructure, personnel and frequent drug stock outs, adherence of clients to the prescribed medicines wouldn't be ensured resulting in poor treatment outcomes of the infected individuals, quick development of resistance and therefore reduced usefulness of these ARV drugs.

These concerns of non adherence have been allayed in such a way that many of the recently published studies have shown over 90% adherence levels across Africa that match or even exceed western standards. We have seen great improvements in the quality of life among people living with HIV (PLWH) and because of the high adherence rates we have not yet seen as much resistance as was anticipated. There is still need for social scientists to explain to us whether these beautiful outcomes could arise from some of our social support structures, such as living in a big family and having many members to support the treatment. Of course we need not be complacent because there are many more reasons for failure other than adherence as explained below. We need to work harder, to identify the issues that have so far helped to make the story of ART successful and strengthen best practices.

Let us now discuss other reasons that could easily make the above rosy picture fuzzy. The factors that can influence development of resistance range from the quality of medicines used, the biology of the Human Immunodeficiency Virus (HIV), the human genetic makeup of the infected individual and chemical reactions such as drug metabolisms in the human liver. In this article, we will concentrate mainly on the HIV viral properties that can lead to resistance and therefore affect usefulness of ART.

In the last few years there has been a rapid rollout of ART that has provided treatment for 3.9 million people in Sub-Saharan Africa alone (WHO Report 2009). In Uganda, ART started being rolled out in 2005 and by the end of 2007 more than 200,000 people had been started on ART.

ART is given in combination of usually three different drugs or classes of drugs. The 2 most common 1st line drugs in Uganda in the recent past were Triomune which is a combination of 3 drugs; stavudine (d4T) plus lamivudine (3TC) and nevirapine (NVP), and Combivir (AZT + 3TC) given with either Nevirapine or Efavirenz. These 2 regimens potentially select for similar resistant viruses in such a way that once one of the combinations has failed the other may also fail. This phenomenon is called cross resistance. Cross resistance is a situation whereby if the virus becomes resistant to one drug, it will sometimes be resistant to similar drugs in the same group. This means that some antiretroviral drugs will not work even if they have not been used before. Cross resistance can limit future treatment options.

As in the example above, most HIV that is resistant to nevirapine is also resistant to efavirenz. One study done in France, reported that 80% of patients who failed on a Nevirapine based regimen also had cross resistance to Efavirenz. .

Cross-resistance is important when you change HIV medications because the health worker needs to choose new drugs that are not cross-resistant to drugs the client has already taken.

Let us examine how resistance develops in HIV. The virus in the human body or cells multiplies very rapidly in such a way that billions of viruses are produced in an HIV infected individual on a daily basis. The body tries to eliminate these viruses but the problem is that it gets overwhelmed by the numbers quickly loosing its foot soldiers (the CD-4 cells) and finally succumbing to AIDS. In this process of rapid multiplication, the virus also makes mistakes which result into its changes in its structure and function and this is called mutation.

When the viruses mutate, then they cannot respond to the drug combinations that are being given to the HIV infected individuals and therefore a client continues to deteriorate even after taking the treatment normally. There are three types of resistance I would want to bring to the attention of readers.

1. Primary resistance; this is the type of resistance which can be inherent in the virus even before it has ever been subjected to any treatment. This can result from the frequent mutations described above.

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DIDANOSINE *continued from Pg 8*

Side Effects

Pancreatitis: the frequency of pancreatitis is dose-related. The drug should be discontinued if there is clinical evidence of pancreatitis. Risk factors include renal failure, alcohol abuse, obesity, history of pancreatitis and concurrent use of Stavudine, Tenofovir (concurrent use no longer recommended), hydroxyurea or allopurinol.

Peripheral Neuropathy: with pain numbness and/or parasthesias in extremities. Frequency is increased significantly when given with Stavudine or hydroxyurea. Onset usually occurs at 2 to 6 months of therapy and may persist if didanosinr is continued despite symptoms.

Gastrointestinal intolerance: especially with buffered tablets and powder are common; abdominal pain, diarrhea, nausea and vomiting

Hepatitis with increased transaminase level

Class adverse effect: Lactic acidosis and severe hepatomegaly with hepatic steatosis caused by mitochondrial toxicity. This complication should be considered in patients with fatigue, abdominal pain, nausea, vomiting, dyspnea. The most frequent cause is didanosine and Stavudine which is nolonger a recommended combination.

Other effects include; rash, marrow suppression, hyperuricemia, hypokalemia, hypomagnesemia, optic neuritis and retinal changes.

Patients on sodium restricted diet: Each gastro-resistant capsule contains 0.53 mg sodium. Careful monitoring is required in patients on a low sodium diet.

Drug Interactions

- Drugs associated with pancreatitis: avoid concomitant use with Stavudine, pentamidine, hydroxyurea
- Buffered formulation: increases the gastric pH thus hindering absorption of drugs that require an acidic medium for absorption. Drugs such as ketoconazole, floroquinolones, indinavir and atazanavir should be taken 1-2 hrs before or after didanosine buffered formulation. Absorption of tetracyclines is also hindered due to the precipitating effect of aluminum and/or magnesium present in the buffered formulation. They should also be taken 1-2 hrs before or after didanosine buffered formulation.
- Alcohol: this should be avoided because it may increase the risk of pancreatitis or liver damage. However, there is no evidence that moderate consumption increases the risk of didanosine induced pancreatitis or hepatotoxicity
- Drugs that cause peripheral neuropathy should be used with caution or avoided, these include Isoniazid, vincristine, ethambutol, cisplatin. Concurrent use with Stavudine and/or hydroxyurea is contraindicated due to high rates of peripheral neuropathy and pancreatitis
- Allopurinol and oral ganciclovir increases Didanosine plasma levels, avoid concomitant use with allopurinol or monitor for Didanosine toxicity and consider dose reduction with ganciclovir

Pregnancy and Lactation

Pregnancy:

Cases of fatal and nonfatal lactic acidosis, with or without pancreatitis, have been reported in pregnant women. It is not known if pregnancy potentiates this effect; however, pregnant women may be at an increased risk of lactic acidosis and liver damage. Hepatic enzymes and electrolytes should be monitored frequently during the 3rd trimester of pregnancy. Use during pregnancy if the potential benefit to the mother outweighs the potential risk of this complication.

Lactation:

Theoreticaly didanosine is expected to be excreted in milk, although the effect on a nursing infant is unknown. However in our setting breast feeding of infants 12 months and below is encouraged.

Storage:

Didanosine capsules and tablets should be kept in their original container tightly closed, and out of reach of children. They should be stored at room temperature below 25°C away from excess heat and moisture.

Didanosine oral solution should be stored in the refrigerator. In areas where access to refrigeration is restricted, the solution should be kept in its original container tightly closed, wrapped in a polythene and kept in a pot of water. The pot may be placed in a basin of sand with water**.** Any unused reconstituted medication should be thrown away after 30 days.

Overdose

There is no known antidote for didanosine overdose. If acute overdose of didanosine occurs, the stomach should be emptied by inducing vomiting or gastric lavage. Supportive and symptomatic treatment should be initiated and the patient should be observed carefully.

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2. Secondary resistance; this is the resistance that develops after a client has been given ART for some time. This is the type of resistance we should jealously guard against. Health programs and HIV positive clients should each play a role in guarding against secondary resistance. Health programs should make sure that drugs are available in their right quantities at the right times. Clients on the other hand should properly adhere to their drugs, taking the drugs in their proper quantities and in the scheduled times, frequently visit the healthcare worker for regular check ups and blood analyses.

3. Transmitted resistance; this arises when an infected individual who is already having any of the 2 resistance patterns above infects his/her partner with an already resistant virus. Healthcare workers are very concerned about this type of resistance. Studies from the developed world presented at the 14th CROI conference in 2007 showed that transmitted resistance was a significant and ongoing problem. Most studies presented then reported rates of resistance of around 10%. The most common type of transmitted resistance was to NNRTIs. Pre-existing resistance mutations lead to higher rates of treatment failure especially when drugs affected by the resistance mutations are used. Given the popularity of NNRTI-based treatment as initial therapy, the fact that NNRTI resistance is the most commonly observed type of resistance transmitted in particularly relevant.

Transmitted resistance can also occur in couples who are both HIV infected because resistant virus can cross from one individual to the other. That is why it so important for HIV positive people and those in discordant couple relationships to continue using condoms consistently and correctly.

In a future article we shall get to discuss the picture in Uganda, the rate at which resistance has developed and any measures the healthcare workers, the Uganda Ministry of Health are taking to prevent and fight this deadly resistance epidemic with in an epidemic.

ASK ATIC

Dr. Stella Zawedde - Muyanja, MBChB

QUESTION

We have a 38-year-old woman who was diagnosed with HIV infection in May 2008 when her husband died of AIDS-related complications. When she was diagnosed, she was symptomatic with oral-oesaphageal candidiasis and extensive weight loss. Her CD4 cell count was 46 cells/mm^3 then.

She was started on septrin prophylaxis, was counseled and prepared for ART. She was started on AZT+3TC+ NVP in June 2008. Her CD4 cell count and Viral Load profile for the last 2 years has been;

MONTH	CD4 CELL COUNT	VIRAL LOAD
June 2008	46	-
December 2008	120	-
June 2009	180	-
December 2009	100	<400 copies/ml
June 2010	60	<400 copies/ml

She has papular pruritic eruptions all over her skin but has no other opportunistic infections. She has no other medical problems and is not on any other long term medication.

Self reported adherence to her ART is very good. She has good family support . She lives with her mother who is also her treatment partner.

Should we change her regimen?

To be continued...

ANSWER

No, we do not need to change her regimen.
Why? You may ask. Let us explore this patients' case further

First we need to point out that initiating Antiretroviral Therapy (ART) for this patient achieved the primary goal of treatment, which is durable suppression of viral replication as evidenced by a Viral Load that is less than 400copies/mL.

Another related and equally critical goal of ART is to reconstitute the immune system—that is, to generate a rise in CD4+ cell count to as near normal levels as possible. Usually, patients experience a rapid rise in CD4+ cell counts within the first few months after initiation of therapy as HIV-1 Viral Load falls, followed by a slower but sustained slow rise in the total count as the naive CD4+ cell population expands.

The expected response is about 100 -150 cells/mm^3 at one year (with baseline levels <350 cells/mm^3) followed by an average of about 50-100 cells/mm^3 /year . CD4 cell counts continue to increase until the 5th or 6th year of treatment when they then taper off.

The immunological response in this patient was very good for the first year but then it became suboptimal in the 2nd year. The most likely explanation for this is that she did not initiate antiretroviral therapy until her CD4+ cell count was very low <100 cells/mm^3 Lower CD4 cell counts at initiation of therapy have been associated with poorer responses to therapy.

Other factors that are associated with suboptimal immune response are;

- Older age at treatment initiation, due to reduced thymic function. The thymus gland which is responsible for formation of mature T lymphocytes atrophies with age resulting in decreased size and activity ,
- Co-infection with HIV-2: NNRTIs e.g. NVP and EFV are largely ineffective against HIV-2 . However co-infection with HIV-2 is more common in West Africa than it is in East Africa.

The first consideration in managing this patient's lack of immune response is whether there is a role for changing her antiretroviral regimen. A second question is whether there are other interventions that can be tried to improve her immune reconstitution.

This patient definitely meets the WHO and Uganda Ministry of Health guidelines definition of immunologic failure to an antiretroviral regimen.

According to WHO and MoH (June 2009), Immunological failure is defined as a fall in CD4 counts of more than 50% on two or more occasions from the on-treatment peak value or persistent CD4 levels below 100 cells/mm^3, in a patient who has been on ART for at least six months or a year.

In the absence of viral load monitoring, any health worker would be justified to change this patient to a second line regimen. In the Ugandan setting, that would be a PI based regimen.

However the presence of Viral Load Monitoring at this Healthcenter changes our approach to this patient. Viral Load monitoring is considered to be the "gold standard" in assessing response to an antiretroviral regimen and has been shown to be superior to CD4cell count monitoring in detecting treatment failure

So in this particular situation, there is no role for changing her antiretroviral regimen.

Our second management consideration would then be to find an intervention that can improve CD4 cell counts. Given her sustained virologic suppression the risk of an AIDS defining illness is lower than in an untreated person. Nevertheless, her low CD4+ cell count places her at increased risk of developing Opportunistic Infections usually associated with suppressed immunity.

One of the newer antiretroviral agents, Maraviroc which belongs to a different class of antiretroviral drugs called CCR5 Inhibitors was studied for its ability to boost CD4+ cell counts in virologically suppressed patients. The results of the clinical trial (ACTG 5256), which was a single-arm pilot study of patients with suboptimal immune reconstitution despite stable virologic suppression for longer than 48 weeks, showed that adding maraviroc to patients' antiretroviral therapy was not associated with clinically meaningful CD4+ cell count increase (defined as > 20 cells/mm^3) at Weeks 22/24.

Unfortunately, there are currently no other accepted clinical strategies for improving immunologic response.

Therefore, the most effective management of this patient is to

- Ensure continued adherence to the current regimen.
- Emphasize the importance of septrin prophylaxis to protect against Opportunistic Infections e.g. PCP Pneumonia and Toxoplasmosis
- Treat any concurrent illnesses e.g. treat the Papular Pruritic eruptions with topical steroid creams and oral antihistmaines.
- Careful monitoring of this patients' viral load. If the viral load becomes detectable (>400 copies /ml on two different occasions) then switching this patient to a second line regimen would be the right course of action.

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