East African Medical Journal Vol. 90 No. 12 (Supplement) December 2013
REASONS FOR CHANGE OF ANTI-RETROVIRAL THERAPY (ART) DRUGS:LOCAL EXPERIENCE
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# REASONS FOR CHANGE OF ANTI-RETROVIRAL THERAPY (ART) DRUGS: LOCAL EXPERIENCE

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## ABSTRACT

***Background*: Highly active anti-retroviral therapy (HAART) reduces morbidity and mortality in HIV/AIDS infected patients. HAART is used indefinitely and the regimens are changed over the course of treatment due to resistance, adverse drug reactions or access to drugs. Few studies have been done in resource constrained setting to assess these factors that have a bearing on compliance and success of treatment.**

***Objective*: To determine the number of patients who changed HAART regimen and reasons for change, their CD4+ cell counts and clinical events in the course of HAART.**

***Design*: A prospective, observational study.**

***Setting*: Kisumu District Hospital and Nairobi Rheumatology Clinic.**

***Subjects*: Twenty nine of the 101 patients who were on HAART.**

***Main Outcome Measures*: Resistance to HAART, adverse drug reactions, change of drugs (HAART) regimen or failed response to HAART regimen.**

***Results*: One hundred and one (60 males and 41 females) patients were screened and initiated on HAART. Twenty nine (12 males and 17 females) were included in the study. The mean age was 41.7 years, mean CD4+ cell count prior HAART initiation was 140.8 cells/$\mu$l. Thirteen patients developed treatment failure on HAART and their mean CD4+ cell count at the 12$^{th}$ month when the drug were changed was 96.5 cells/$\mu$l. Five patients developed neuropathy, one developed lipodystrophy, one ART related liver injury, three pancreatitis, four changed due to cost and one due to Steven Johnson syndrome. Thirteen patients had resistance to HAART and ten of the 13 had new clinical events: - cryptococcous meningitis, pulmonary tuberculosis, cytomegalovirus (CMV), herpes zoster virus (HZV), pneumocystis jiroveci pneumonia and chronic diarrhoea. Five patients had a documented high HIV-RNA viral load mean of 619,919.5 copies/ ml (5.792 log units) at the time of changing HAART at 12 months. Eight of the 13 did not have HIV-RNA viral load due to high cost.**

***Conclusion*: Reasons for Changing HAART included: cost of HAART, Poor tolerability Toxicities (neuropathy, and lipodystrophy, anti-retroviral related liver injury (ARLI), Steven Johnson Syndrome, pancreatitis) and probable failure of to HAART. CD4+ cell count was declining in the HAART resistance group. Failing response to HAART in routine clinical practice is recognised. Effort must be made to put in place resistance surveillance without HAART, CD4+ cell count, HIV viral load and clinical assessment are in patients on parameters to consider when changing treatment.**

## INTRODUCTION

Since the introduction of highly active anti-retroviral therapy (HAART) for management of HIV/AIDS a decade ago, the morbidity and mortality secondary to HIV/AIDS have declined dramatically. Indeed, HAART has transformed HIV disease into a chronic illness requiring long term medical management and close follow up (1).

Once initiated, patients generally remain on HAART medications indefinitely. Since resistance to HAART is known to occur, there is a risk of transmitting a drug resistant virus variant hence the necessity to carry out close monitoring of patients. In resource constrained setting with the highest burden of HIV/AIDS, little work is done to assess the risk of HAART resistance and reasons for change in real clinical practice. Patients usually present in late stage HIV/AIDS with low CD4+ cell counts, single or multiple opportunistic infections, wasting and poor Karnofsky performance score (2).

## MATERIALS AND METHODS

Three hundred and sixty three patients (222 males and 141 females) who were HIV positive were screened for the study. Two hundred and sixty two (162 males and 100 females) patients were excluded (referred to Mission Hospitals, Provincial General Hospital (PGH) Kisumu, Kenyatta National Hospital (KNH) comprehensive care clinic as requested). The patients were followed up over one year.

One hundred and one patients (60 males and 41 females) who were on HAART and HIV care were included and followed up. The ethics and standards committee of Kisumu District Hospital approved the study. The study was done at a time when the free access ART project by the ministry of health had not been rolled out to peripheral medical facilities in the country. These are patients who were able to afford HAART and the clinical care was done by one of the medical doctor (authors). Informed signed consent was obtained form each patient.

They were examined by one of the authors on every visit or when the condition worsened or they developed a new medical condition. Counselling was sustained for all the patients to ensure compliance to all drugs and clinic attendance.

Under aseptic technique, 10 mls of blood was drawn from the cubital fossa and used for assessment of the following immunological and biochemical parameters every three months:- CD4+ cell counts, complete blood count, liver function tests, urea, electrolytes, and creatinine. The patients were physically examined for weight loss/gain, lipodystrophy, skin rashes, jaundice or any new clinical event.

These were strict criteria hence left out some patients who could afford the immunological and biochemical follow up every six months (which is considered a poor monitoring technique especially for the severely immunosuppressed patients).

The CD4+ cell count was done using the FACS (fluorescent activated cell sorter) flow cytometry machine with a sensitivity of 1-2000 cells/$\mu$l. Serum amylases and lipase was done for those who had pancreatitis.

Complete blood count was analysed using the coulter counter machine.

Blood sugar was analysed using the glucometer, ACCU-chek ® GO (Roche diagnostics GmbH, D-68298 Mannheim, Germany), biochemical tests were done thus (AST and ALT by reverse passive heamagglutination test (RPHA), Alkaline phosphatase and bilirubin and urea and electrolytes by calorimetric method). The weight (Kg) and height (cm) of the patients were also taken.

Three patients had pancreatitis and their serum amylase and lipase levels were assessed.

The median follow up time was one and half years and the follow up is still on.

The HAART combinations used were combivir/efavirenz and EMTRI 30/40 ( fixed dose combination of lamivudine, nevirapine and stavudine), or efavirenz, videx and zerit.

All the 101 patients had data for one year (CD4+ cell count, complete blood count, clinical data) and were thus analysable.

*Intervention*: HAART was changed appropriately to second line. HAART was either:

(i) appropriately changed to second line where there was failed response, lipodystrophy, neuropathy or cost implications.

(ii) stopped in Steven-Johnson syndrome, pancreatitis and ARLI; the condition managed conservatively, then HAART appropriately changed when the patients had improved.

## RESULTS

Twenty nine (12 males and 17 females) out of 101 patients were included in the analysis as patients

who had to change treatment.

The male: female ratio of the patients who changed the treatment was 1:1.9. Their mean age was 41.7 years. The mean CD4+ cell count prior HAART initiation was 140.8 cells/μl (12-433). Nine patients developed neuropathy at six and nine months respectively. One patient had lipodystrophy at nine months.

| Year starting HAART | No. of patients |
|---|---|
| 2001 | 16 |
| 2002 | 20 |
| 2003 | 33 |
| 2004 | 20 |
| 2005 | 8 |
| 2006 | 4 |

HAART combinations used.
*EMTRI 30/40*
*COMBIVIR*/EFAVIRENZ
D4T/ddI/EFAVIRENZ

**Table 1**

*Shows adverse conditions, reason for change, number of patients and ART regimen used.*

| Condition | No. of patients | ART regimen used |
|---|---|---|
| Declining CD4+ cell count | 13 | EMTRI 30/40 |
| Neuropathy | 5 | EMTRI 30/40 |
| Lipodystrophy | 1 | EMTRI 40 |
| Cost | 4 | *Combivir*/ efavirenz |
| ARLI | 1 | EMTRI 40 |
| Pancreatitis | 3 | 2 EMTRI 30, 1 *combivir*/ efavirenz |
| Steven Johnson syndrome | 2 | Combivir/ efavirenz |

Combivir-(Lamivudine+Didanosine)

## DISCUSSION

In most cases, HAART results in a reduction in plasma viral load to below the limit of detection. Regardless of the decrease in morbidity and mortality associated with HAART regimens and the significant increase in the life expectancy of treated HIV-infected individuals, eventual failure of therapy is common and poses challenges for future treatment.

Changing HAART regimen is often necessary because of both acute and chronic toxicities, concomitant new clinical conditions and development of virologic failure (3).

The five patients who had neuropathy and lipodystrophy had appropriate mean CD4+ cell count response of 104.6, 185.1, 250.8, 321 and 335 cells/μl at zero, three, six, nine and 12 months respectively. The drug change was necessitated by the adverse event. Pancreatitis and lipodystrophy (loss of subcutaneous fat in the face, extremities and buttocks) has been associated with stavudine, while Steven Johnson syndrome, Nevirapine (1%) and Efavirenz (0.1%) and is life threatening (3-5).

Four patients changed drugs due to cost. They were on combivir/efavirenz combination and were referred to mission hospitals for change to the generic formulations, which are affordable. Their compliance or effective response was therefore questionable as evidenced by the declining mean CD4+ cell counts of 141.1, 372.1, 235.6, 200.7 and 101.4 cells/μl at zero, three, six, nine and 12 months respectively. Some patients could have missed their doses though they consented to compliance with treatment. There is no available simple test, for example, urine or saliva test to quantify and prove compliance to ARTs. Urine test for Lamivudine compliance is still under study (12).

Thirteen patients changed drugs due to declining CD4 + cell counts. The CD4+ cells declined from a mean of 155.2 cells/μl at initiation (zero month) to 142.8, 180.4, 131.3 to 96.5 cells/μl at three, six, nine and 12 months respectively. While CD4+ cell counts should ideally be done every three months, most patient support centres and HIV care clinics test it every six months. This may lead to clinical deterioration before the patient is identified early enough. The CD4+ cell count decline was evident from the 9$^{th}$ month.

There were also concomitant new clinical events noted: cryptococcous meningitis 2, chronic diarrhoea due to cryptosporidium 1, herpes zoster virus (HZV) 2, cytomegalovirus (CMV) 1, severe wasting syndrome 2, tuberculosis (PTB and extrapulmonary) 3 and pneumocystis jiroveci pneumonia (PJP) 2. The CD4+ cell count decline and new clinical events are surrogate markers of resistance to HAART. Due to

high cost, it was impossible to do HIV-RNA viral load for all the patients. Only 5/13 did the HIV viral load at the time of changing the drugs and the mean HIV viral load was 619,919.5 virions/ml (5.7921 log units). This demonstrated distinct virological failure. Virologic failure is defined as HIV RNA > 400 copies at 24 weeks of therapy, HIV RNA copies of > 50 copies/ml at 48 weeks of HAART or repeated detection of vireamia after virologic suppression (6). In Africa, HIV resistance testing was reported in just five studies and suggested resistance mutations in 71 of 594 patients (12%). Most of the resistance mutations were to non nucleoside reverse transcriptase inhibitors (NRTIs) and was mostly 184V (7).

HIV-RNA viral load assessment is rarely done due to high cost (except in CDC and AMPATH sponsored HIV care health facilities). In patients with very low CD4+ cell counts like the ones in this cohort, it was not clear whether they had secondary resistance once HAART was initiated or they had acquired a virus which was already resistant to HAART (primary resistance). While the change of HAART depended on declining CD4+ cell counts, a surrogate marker of higher HIV viral load, clinical deterioration and new clinical events (Tuberculosis, cryptococcous meningitis, CMV, and cryptosporidium), it has also been observed that there are patients whose CD4+ cell counts remain low despite adequate HIV-viral suppression. This low CD4+ cell count regeneration has been associated with a reduced thymic production of the CD4+ cells (11).

The failure of HAART most likely arises from a combination of viral and host factors that facilitate the emergence of HIV variants with resistance to multiple anti-retroviral drugs. The emergence of drug resistance in patients receiving HAART can be primarily attributed to the high spontaneous mutation rate and high rate of HIV turnover in HIV-infected individuals, selective pressure arising from anti-retroviral therapy, pharmacokinetic characteristics of anti-retroviral drugs, patient tolerance/adherence to anti-retroviral regimens and the existence of viral reservoirs (15).

Factors independently associated with a greater risk of HIV resistance mutations include (8):

(i) Young age <45 years,
(ii) CD4+ cell counts, < 200 cells/$\mu$l at HAART initiation,
(iii) HIV viral load > 100,000 copies/ml at HAART initiation
(iv) HIV exposure route which was unknown or other than sexual/intravenous drug users (IVDU) routes
(v) A previous AIDS diagnosis
(vi) An unboosted PI-based regimen and
(vii) Triple nucleoside therapy.

HAART can be feasibly administered in resource-constrained settings and close monitoring is key to success of HAART (7). Most of the patients 23/29 (79.3%) had been initiated on *EMTRI 30/40* (Nevirapine, Stavudine and Lamivudine fixed dose combination). Studies have shown that, in severely immunocompromised, anti-retroviral-naïve, HIV–1 infected patients, treatment with efavirenz based regimen compared with a non-boosted PI-based regimen resulted in a superior virologic response with no difference in immunologic or clinical effectiveness (9, 10). Adherence and compliance to HAART is key to reducing resistance and treatment/segmen success.

In this cohort, patients presented late with low mean CD4+ cell counts of 140.8 cells/$\mu$l , young age <45 years and this could predispose to ART resistance. There were signs of resistance very early in the course of treatment at nine months evidenced by declining CD4+ cell counts. This could be due to their late presentation when they are very sick or they may have acquired a mutant HIV-strain with primary resistance.

Patient adherence is a highly important factor in the effectiveness of anti-retroviral regimens. Adherence to treatment could be monitored by estimation of ART drugs in biological fluids. Indeed, a study confirmed the sensitivity and usefulness of monitoring urine lamivudine levels in spot specimens to monitor patient adherence (12). This will otherwise await large clinical trials to confirm it's sensitivity.

Currently available approaches to measure adherence include:

(i) patients' self-report
(ii) Physician assessments
(iii) electronic monitoring
(iv) pill count and
(v) prescription refill compliance (13).

Though these methods have proved useful with predictive outcomes, the results are variable (13, 14). HIV resistance surveillance in resource-constrained setting is key before it gets overwhelming. Questions arising from this scenario are: (i) do patients with very low CD4+ cell counts require HAART resistance

testing prior HAART initiation (per patient/ community survey in HIV endemic areas) since they will soon switch drugs? and (ii) do the resource constrained settings require more potent drugs compared to what is in use currently to salvage the very sick patients?

*What this paper adds*

(i) It documents HAART faiure in routine clinical practice in Kenya.
(ii) It emphasises the need to have HIV resistance surveillance in resource constrained setting before it gets overwhelming.
(iii) In this cohort, patients developed HAART failure very early at nine months.

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