Response to First Line HAART using CD4 Cell Counts

Experience in a University Hospital in Kingston

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ABSTRACT

Objectives: *To assess the extent to which the current practice for first line therapy concurs with the recommended guidelines and to examine the response of treatment naïve patients to first line Highly Active Antiretroviral Therapy (HAART) at the University Hospital of the West Indies, using CD4 cell counts.*

Methods: *Over a three-month period, a cross-sectional study design was instituted and data were collected on all patients on HAART at the University Hospital of the West Indies (UHWI) outpatient HIV clinic. Information was collected by reviewing patient medical records using data collection sheets. The data obtained from the medical records included: age, gender, date of diagnosis of HIV, date at which HAART was commenced, CD4 cell counts prior to the commencement of antiretrovirals, the initial HAART regimes and subsequent CD4 cell counts.*

Results: *A total of 165 persons who met the criteria of being on HAART therapy were enrolled in the study. The average time span between diagnosis of HIV and commencement of antiretroviral therapy was 1.92 years and the range for this was 0 to 12.29 years. The average CD4 count prior to initiation of HAART was 186 cells/mm^3. The most common regime used at the UHWI for first line therapy was combivir and efavirenz, n = 78 (47.3%), followed by combivir and nevirapine, n = 29 (17.6%). The average difference between the initial CD4 count prior to the initiation of HAART and first repeated CD4 count was 102 cells/mm^3. The mean time between the first and repeated CD4 cell counts was 376 days.*

Conclusion: *The recommended guidelines were adhered to for the majority of patients initiated on antiretrovirals at the UHWI. The treatment outcomes achieved at the UHWI were similar to those achieved in developed countries. This gives substantial evidence in support of international efforts to make antiretroviral therapy available in developing countries.*

Key words: CD4, HAART, HIV

Respuesta a la Terapia TARGA de Primera Línea Usando Conteos CD4

Experiencia en el Hospital Universitario en Kingston

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RESUMEN

Objetivos: *Evaluar hasta que punto la práctica actual de la terapia de primera línea concuerda con las normas recomendadas y examinar la respuesta al tratamiento por parte de los pacientes nunca antes sometidos a la terapia antiretroviral altamente activa, (TARGA) en el Hospital Universitario, usando conteos de células CD4.*

Métodos: *Por un periodo de tres meses, se instituyó un diseño de estudio transversal, y se recogieron datos de todos los pacientes sometidos a TARGA en la clínica de VIH para pacientes externos en el Hospital Universitario de West Indies (UHWI). La información fue obtenida revisando las historias clínicas de todos pacientes, usando hojas de recogida de datos. Los datos obtenidos de las historias*

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clínicas incluían: edad, género, fecha de diagnóstico de VIH, fecha de comienzo de TARGA, conteo de células CD4 antes del comienzo de los antiretrovirales, los regimenes iniciales de TARGA y los subsecuentes conteos de células CD4.

Resultados: *Un total de 165 personas que satisfacían los criterios de la terapia TARGA fueron enroladas en el estudio. El tiempo promedio que medió entre el diagnóstico de VIH y el comienzo de la terapia antiretroviral fue 1.92 años, en tanto el rango para esta fue de 0 a 12.29 años. El conteo promedio de conteo de CD4 antes del comienzo de TARGA fue 186 células/mm3. El régimen más común usado en UHWI para la terapia de primera línea fue combivir y efavirenz, n = 78 (47.3%), seguido por el combivir y nevirapine, n = 29 (17.6%). La diferencia promedio entre el conteo inicial de CD4 antes del comienzo de TARGA y el primer conteo repetido de CD4 fue 102 células/mm3. El tiempo promedio entre los primeros conteos CD4 y los repetidos fue 376 días.*

Conclusión: *Se siguieron las normas recomendadas en relación con la mayoría de los pacientes iniciados en el tratamiento con antiretrovirales en UHWI. Los resultados del tratamiento logrados en UHWI fueron similares a los logrados en los países desarrollados. Esto ofrece sólidas evidencias en apoyo a los esfuerzos internacionales por poner la terapia antiretroviral a disposición de los países en vías de desarrollo.*

Palabras claves: CD4, TARGA, VIH

West Indian Med J 2010; 59 (4): 440

INTRODUCTION

Since the introduction of Highly Active Antiretroviral Therapy (HAART), there has been a significant reduction in the morbidity and mortality associated with Human Immunodeficiency Virus (HIV) infection (1).

HAART refers to the use of a combination of three or more antiretrovirals usually spanning at least two classes. There are six classes of antiretroviral agents. These antiretroviral drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI) inhibit reverse transcription by being incorporated into the newly synthesized viral DNA and preventing its further elongation, examples are lamivudine/zidovudine (combivir) and stavudine. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) inhibit reverse transcriptase directly by binding to the enzyme and interfering with its function, examples are efavirenz and nevirapine. Protease inhibitors (PIs) target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for final assembly of new virons, examples of these are lopinavir/ritonavir (Kaletra), indinavir and nelfinavir. Integrase Strand Transfer Inhibitors (INSTI) such as raltegravir inhibit the enzyme integrase which is responsible for integration of viral DNA into the DNA of the infected cell. Fusion and Entry Inhibitors (enfuvirtide and maraviroc, respectively) interfere with binding, fusion and entry of HIV-1 into the host cell by blocking one of several targets.

The goals of treatment are to reduce HIV-related morbidity and prolong survival, improve quality of life, restore and preserve immunologic function, maximally and durably suppress viral load and prevent HIV transmission (2).

Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 cell count < 350 cells/mm^3. Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 cell count: pregnant women patients with HIV-associated nephropathy and patients co-infected with HBV, when treatment is indicated (2). Appropriate use of ARVs leads to suppression of virologic replication and an increase in CD4 cell count.

The Jamaican Experience

Antiretroviral drugs (ARVS) were introduced to Jamaica in 1988. At the time of their introduction, the cost was prohibitive and was far out of reach of many persons living with HIV/AIDS. Consequently, the early experience with these medications are limited to the relatively small number of patients who could afford to purchase the medications or those who could access them abroad. This resulted in a high mortality rate among persons living with HIV/AIDS. The number of AIDS deaths in Jamaica peaked at 692 in 2002 (3). There was also the additional challenge of the unavailability of specific blood investigations necessary to monitor these patients. In developed countries, fairly expensive laboratory tests are used to assess the progression of HIV/AIDS to guide clinical decisions about commencement and modification of therapy. Tests that have been used for these purposes are the T-helper inducer cell (CD4) count, the plasma HIV RNA (viral load), genotype and phenotype resistance testing. In the absence of these clinical resources, clinicians had to find other means of assessing patients with HIV. Among the measures that were used was the total lymphocyte count which is suggested to be loosely equated to the CD4 cell count.

In addition, the presence of AIDS defining illnesses, significant weight loss and certain mucocutaneous disorders have been used as crude indicators of immune status.

In the year 2004, as a result of Government initiatives and the presence of the Global Fund to fight AIDS, Tuber-

culosis and Malaria (GFTAM), the cost of ARVs was highly subsidized and thus became affordable for many persons living with HIV/AIDS. Additionally, tests to monitor patients' response also became more accessible. At the time of this paper, patients are able to get ARVs, CD4 counts and plasma HIV RNA testing on a three monthly and six monthly basis respectively, at no cost. This has coincided with a dramatic fall in the Jamaican mortality associated with AIDS (3).

Against this background, it is now possible for us to examine Jamaican patients' response to the use of HAART using international standards.

HAART in Jamaica

Regimes that contain two NRTIs with either, an NNRTI, a ritonavir-boosted PI or an Integrase Strand Transfer Inhibitor (INSTI) are recommended as first-line therapy (2). However, in resource limited settings such as the Caribbean, where PIs and INSTIs are not readily available, the recommended first line regime consists of two NRTIs with a NNRTI, unless otherwise contraindicated. Protease inhibitors are reserved for second and third line regimes. This is outlined in Jamaica's Ministry of Health Guidelines for treating HIV (4).

This paper will assess the extent to which the current practice for first line therapy coincides with the recommended guidelines. It will also examine the response of treatment naïve patients to first line HAART at the University Hospital of the West Indies (UHWI), using CD4 cell counts.

SUBJECTS AND METHODS

Approval was obtained from the Faculty of Medical Sciences, The University of the West Indies/University Hospital of the West Indies Ethics Committee, Jamaica. All patients on antiretroviral therapy enrolled at the UHWI outpatient HIV clinic were included in this study.

A cross-sectional study design was instituted and data collection occurred during January until March 2009. Information was collected by reviewing patient medical records using data collection sheets. The data obtained from the medical records included: age, gender, date of diagnosis of HIV, date at which HAART was commenced, CD4 cell counts prior to the commencement of antiretrovirals, the initial HAART regimes and subsequent CD4 cell counts. These data were collected by a research nurse and information was stored in a safe and secure environment, so as to protect the confidentiality of the study participants.

The data were analysed using SPSS version 8. Means with standard deviations were used to describe central tendency and distribution of all variables. The one way Anova test was used to estimate differences between HAART regime groups.

RESULTS

A total of 165 persons who met the criteria of being on HAART therapy were enrolled in the study. The mean age was 36.57 years and patients ranged from 20 years to 63 years. The male to female ratio was 1: 1.35 (n = 69 and 93 respectively) [Table 1].

The average time span between diagnosis of HIV and commencement of antiretroviral therapy was 1.92 years and the range for this was 0 to 12.29 years. The average CD4 count prior to initiation of HAART was 186 cells/mm^3.

The most common regime used at the UHWI for first line therapy was combivir and efavirenz, n = 78 (47.3%), followed by combivir and nevirapine, n = 29 (17.6%), combivir and indinavir, n = 13, (7.9%), and stavudine, lamivudine and efavirenz, n = 13 (7.9%) [Table 1].

The number of patients that were switched to other regimes 1, 2, 3 and 4 times were 86, 46, 22 and 5, respectively.

Table 1: Frequency of the first line HAART used in study population

	Frequency	**Per cent**
	1	0.6
Combivir and nevirapine	29	17.6
Stavudine, lamivudine, indinavir	1	0.6
Combivir, nelfinavir	1	0.6
Lamivudine, stavudine, nelfinavir	2	1.2
Incorrect regime (other)	19	11.5
Combivir and efavirenz	78	47.3
Stavudine, lamivudine, nevirapine	4	2.4
Stavudine, lamivudine, efavirenz	13	7.9
Combivir, lopinavir/ritonavir	1	.6
Combivir, indinavir	13	7.9
AZT	3	1.8
Total	**165**	**100.0**

The average difference between the initial CD4 count prior to commencing HAART and first repeated CD4 count was 102 cells/mm^3 (Table 2).

Table 2: Interval increase in CD4 counts of study population

Mean difference between 1st and 2nd CD4 cells/ mm^3		102.1
95% Confidence Interval for Mean	Lower Bound	120.9
	Upper Bound	83.4

The mean time between the first and repeated CD4 cell counts was 376 days (Table 3).

The rise in CD4 count was examined with regards to the initial HAART regime. The highest rise was seen when combivir was used with indinavir as a starting regime (153.5 cells/mm^3). This was followed by stavudine, lamivudine and efavirenz (151.0cells/mm^3) and Combivir and nevirapine (130.4cells/mm^3) (Table 4).

Table 3: Time interval in days between first and repeated CD4 count

Time		Days
Mean time between 1st and 2nd CD4 cell counts (days)		375.9
95% Confidence Interval for Mean	Lower Bound	326.7
	Upper Bound	425.1

Table 4: Increase in CD4 counts with various first line HAART regimes

	n	Mean	SD
Combivir and nevirapine	21	130.3	85.6
Combivir and efavirenz	61	91.5	90.5
Stavudine, lamivudine and efavirenz	10	151.1	201.6
Combivir and indinavir	11	153.5	141.5
Other	16	53.5	38.7
Total	**119**	**104.0**	**106.6**

When compared, the CD4 cell count increase was greater with the combination of stavudine, zidovudine and efavirenz than with lamivudine, zidovudine and efavirenz (151.1 v 91.5). The lowest CD4 cell count increases were seen when a non-recommended regime, such as montherapy or dual therapy, was used (53.5 cells/mm^3).

DISCUSSION

The WHO guidelines for the use of HAART in resource limited settings state that for first line therapy, a combination of two NRTIs and one NNRTI should be used. This is as a result of the lack of availability and high cost of the other classes of antiretrovirals. In developed countries, first line therapy may also include a protease inhibitor or an integrase strand transfer inhibitor regime.

Previous studies have indicated that CD4 cell count increases are generally expected to be greater in patients commenced on boosted PI regimes when compared to NNRTI-based regime. However, NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve prevalence of NNRTI-resistant viral strains in treatment-naïve patients (5–8) and the low genetic barrier of NNRTIs for development of resistance.

Despite the high incidence of resistance to efavirenz, many large randomized, controlled trials and cohort studies of treatment-naïve patients have shown potent viral suppression in efavirenz-treated patients; a large proportion of these patients had HIV RNA < 50 copies/ml during up to 7 years of follow-up (9–10). Studies that compared efavirenz-based regimens with other regimens have de-monstrated that the combination of efavirenz with two NRTIs was superior virologically to some PI-based regimens, including indinavir (11), lopinavir/ritonavir (12) and nelfinavir (13), and to triple-NRTI–based regimens (8–14).

However, many studies have shown that the efficacy of a starting regime of PI or NNRTI is similar. The FIRST (Flexible Initial Retrovirus Suppressive Therapies) study done in the USA, which was carried out by Community Programs for Clinical Research on AIDS (CPCRA), a federally funded national network of community-based research groups, showed no significant differences in the composite endpoint of disease progression (AIDS or death) or a CD4 cell count of less than 200 cells/mm^3 between the NNRTI and the PI (15).

In comparing the NNRTIs, efavirenz and nevirapine, the non-nucleoside (*2 NN study*) was a landmark trial. They found that there was no statistically significant difference between the two drugs with regard to viral suppression or CD4 cell count increases. There were differences in the rates of adverse events however, with hepatotoxicity and mucocutaneous rash occurring more in the nevirapine arm (28). This is of significance in Jamaica and other developing countries where cost and affordability are major limiting factors, Protease inhibitors are not readily available and are reserved for persons failing regimes containing NNRTI or where there has been significant toxicity or an absolute contraindication to the use of a NNRTI.

The majority of the patients at the UHWI outpatient HIV clinic, 75.2% (n = 124), were commenced on a NNRTI based regime. Efavirenz (55.2%) was used more frequently than nevirapine (20%) as initial therapy. The NRTI back bone used in combination with efavirenz included: 85.6% combivir/efavirenz and 14.4% stavudine/lamivudine/efavirenz.

In the present study, the baseline mean CD4 count at which HAART was initiated was 186 cells/mm^3. The recommended CD4 threshold for commencing HAART is 350 cells/mm^3. Studies have however shown that a good immunological response to HAART can be achieved regardless of the CD4 count at initiation of therapy (16–18) and there are data to suggest that maintenance of CD4 counts continues through year five of therapy in patients who achieve ongoing viral suppression (19–20).

In the patients at the UHWI, there was a mean rise in the CD4 cells of > 100 cells/mm^3 after a mean of 12-months. In a study done in Haiti, another developing country in the Caribbean, 1004 treatment naïve patients were enrolled in a study where first line NNRTI based regime was initiated. The patients studied had an AIDS-defining illness or a CD4 cell count under 200 cells/mm^3. There was a median increase in the CD4 cell count at 12 months of 163 cells/mm^3 (interquartile range, 77 to 251 cells/mm^3) [21]. In a meta-analysis of clinical trials involving treatment naïve adults who received a NNRTI based regime, the mean increase in the CD4 cell count was 174cells/mm^3 over approximately 12 months (22, 23).

Similarly, an analysis of the 12-month outcome of treatment naïve patients started on both NNRTI and PI-based regimes in 2001 and 2002, in a Baltimore clinic, found a

mean increase in the CD4 cell count of 139 cells/mm^3 over one year (24, 25).

In the present study, the CD4 response over twelve months was lowest in those patients initiated on regimes not consistent with the recommended guidelines; patients prescribed monotherapy and dual therapy, 11.5% (n = 16), had a mean increase of 53.56 cells/mm^3 over 12-months. This marked difference was statistically significant (p = 0.037). On the other hand, the highest response, a rise of 153.54 cells/mm^3, was seen in patients started on combivir and indinavir. This was followed by stavudine, lamivudine and efavirenz (151 cells/mm^3), combivir and nevirapine (130.4 cells/mm^3) and 91.5 cells/mm^3 was seen with patients started on combivir and efavirenz.

Stavudine was initiated in 20 patients in this study. However, stavudine is no longer a preferred option used to commence HAART therapy. Despite its relatively low cost, leading to its continued use in developing countries, it has significant adverse reactions which have caused it to be removed from recommended guidelines in first world countries. Adverse reactions associated with stavudine include peripheral neuropathy, lactic acidosis and lipoatrophy.

Other studies have also compared stavudine and zidovudine, and found increased risks of disease progression and death in the stavudine containing arm (26–27).

The level of adherence to the prescribed HAART in this study was not assessed. An assessment of adherence done at the University Hospital of the West Indies showed that the mean levels were as follows: 87.66% self-report for tablets, 88.70% self-report for dosing frequency, 87.02% social worker/nurse report for tablets and 88.10% social worker/nurse report for dosing frequency (28). Good adherence, however, is defined as 95% or greater and patients below this level were classified as being non-adherent (29). Thus, on this background, we can expect that the CD4 response in this population is negatively affected by non-adherence and thus efficacy of a prescribed regime cannot be accurately assessed.

This study has some limitations. Reasons for noncompliance with the recommended guidelines should have been elucidated. This would not only provide explanations for the given regime but would also allow for focussed intervention in correcting errors in current prescribing practices. Also, as this was a retrospective review of records, the timing of the CD4 counts being done was not standardized and this might have affected the results. The level of adherence to the prescribed HAART was also not assessed but treatment response might have been a function of both adherence and the therapeutic efficacy of the medications prescribed. This limits one's ability to compare the therapeutic benefits of the different medications. Finally, in some instances, very few patients were prescribed particular treatment regimens. This limits the generalizability of the findings related to these medications.

In summary, the recommended guidelines were adhered to for the majority of patients initiated on antiretrovirals at the UHWI. The treatment outcomes achieved at the UHWI were similar to those achieved in developed countries. This gives substantial evidence in support of international efforts to make antiretroviral therapy available in developing countries.

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