Neurocognitive correlates of the use of combined Antiretroviral Therapy among HIV-infected adults attending care and treatment center at Muhimbili National Hospital, Dar es Salaam, Tanzania: An analytical cross-sectional study

Azan Abubakar Nyundo[1], David Musyimi Ndetei[2,3], Caleb Joseph Othieno[2], Anna Muthoni Mathai[2]

[1]Department of Internal Medicine and Child Health (Psychiatry Division), University of Dodoma, Dodoma, Tanzania
[2]Department of Psychiatry, College of Health Science, University of Nairobi, Nairobi, Kenya
[3]African Mental Health Foundation, Nairobi, Kenya

Correspondence to
Dr. Azan A. Nyundo
University of Dodoma
P.O. Box 395
Dodoma, Tanzania
azannaj@gmail.com

Abstract

Background
The discovery of the highly active antiretroviral therapy has improved the life span of people living with HIV/AIDS (PLWHA) to almost that of the general population. This, however, has been coupled with increased incidences of HIV-associated dementia, especially mild cognitive impairment. Combined antiretroviral therapy (cART) has been observed to improve neurocognitive functions but the ART regimen that is best suited for improvement of neurocognitive functions is still largely unknown. This study was aimed at determining how neurocognitive deficits in patients on cART were related to ART regimen.

Methods
This was a cross-sectional analytical study. A sample of 351 adult patients attending care and treatment center (CTC) at Muhimbili National Hospital (MNH) in Dar es salaam, Tanzania were screened for HIV-associated neurocognitive deficits (HAND) against the ART regimens the patients were using. The study that was conducted from July to August 2012 and employed a standardized tool known as International HIV Dementia Scale (IHDS). Analysis was done using SPSS version 18. Frequency distribution, Chi-square, Fisher's exact test and multivariate regression analysis were calculated to determine the levels of risk which was set at 5% significance level ($p < 0.05$).

Results
Two hundred and forty of the 351 (68.4%) patients screened positive for neurocognitive deficits. Under descriptive statistics, factors such as age, years of formal education, central nervous system penetration effectiveness (CPE) score and the use of efavirenz containing regimens showed statistically significant association with HAND at $p=0.03$, $p=0.038$, $p<0.001$ and $p=0.039$, respectively, while on multivariate analysis only ART combination with CPE based on 2010 scoring system showed significant association system ($p=0.02$, AOR=0.449 and C.I=0.27-0.748) with HAND.

Conclusion
These findings support the hypothesis that specific ART factors such as CPE may be protective against neurocognitive deficits. The study also highlights the need to choose appropriate ART regimen with special consideration to their potential neurotoxic side effect. Individual assessment for best therapeutic response is crucial for the patients' cognitive wellbeing.

Key words
HIV-associated neurocognitive deficits (HAND), Antiretroviral, Central nervous system penetration, Muhimbili National Hospital, Dar es Salaam, Tanzania

Introduction

The advent of highly active antiretroviral therapy (HAART) has prolonged the life span of people living with HIV and AIDS (PLWHA) to almost that of the general population; (1) however, high prevalence of HIV-related neurocognitive impairment continues to be reported, particularly in the form of mild cognitive impairment (2). Neurocognition refers to the sum of all functions of the CNS ranging from simple processes such as sensation to the more complicated higher functions such as memory-processing, thinking, motor functions, psychomotor functions and other executive functions. HIV-associated neurocognitive deficits (HAND) refers to impaired neurocognition that is attributed to HIV infections.
With HAART in the form of combined antiretroviral therapy (cART), severe forms of HAND are now rare manifestations among those with HIV infection, though milder forms of neurocognitive impairments that hinder daily independent functioning are still prevalent among PLWHA (3). HAART has largely been observed to improve neurocognitive functions or even prevent further escalation from milder to a more severe and lethal form known as HIV dementia which has relatively higher mortality rate (4).

Though the mechanism of action is still not very clear, the use of cART appears to improve both immunological and cognitive functions among PLWHA (5). It has also been reported that benefits may be maximized when initiation of an ART is well timed, preferably at relatively earlier stages of HIV/AIDS (6-7).

Among the few factors that have been explored regarding how ART curbs neurocognitive impairment is the CNS penetration effectiveness (CPE), which refers to the ability of an ART to reach the CNS through the blood brain barrier. In this study, the revised 2010 CPE ranking system developed by Latendre and others was used to estimate penetration effectiveness of individual or combined ART regimen (8) (see Table I). This scoring system was developed on the basis of the pharmacokinetic and pharmacodynamic profile of the specific ART regimens and has proven useful in predicting which particular cART suppresses HIV1 viral RNA concentration in the CSF and plasma (9).
CPE has of recent been implicated as a protective factor against development of HAND (9), It is theorized that once the drug reaches the CNS it will mitigate the pathogenic process of HIV by preventing viral replication and neuronal damage that may eventually lead to onset of neurocognitive impairment (10-11). ARVs with higher CPE score tend to improve neurocognitive deficits more so than those with lower CPE scores (9).
Pathogenesis of HIV in the CNS is multifaceted but evidence suggests that HIV-infected monocytes and T-cells produce a pro-inflammatory cascade that may be responsible for dysfunction and cell death clinically manifesting as HAND(12). cART with good access to the CNS is thought to halt this process and mitigate its effects including the development of HAND (13). Furthermore,

ART regimens with higher CPE score have been shown to reduce both plasma and CSF viral load to undetectable levels compared to ART regimens with lower CPE score which may have undetectable plasma but significant CSF viral concentration (11)(14).
It has, however, been observed that some of the ART regimens have been linked with poorer neurocognitive performance outcomes, despite having higher CPE scores (15) (16). It is hypothesized that despite their high CPE score, these antiretroviral drugs may have potential for neurotoxicity (17-24). One of the proposed mechanisms to explain the development of HAND among those on cART with good CNS penetration is that some of the ART regimens may induce oxidative stress leading to accumulation of neurotoxic free radicals which manifest clinically as HAND (18).
It is important to note that there are other non-pharmacological factors that may be linked to neurocognitive performance amongst PLWHA. These include age, level of education, WHO clinical staging and the presence of other chronic medical or surgical illnesses that may interfere with brain function.
Our study aimed at determining the association between use of ARVs and presence of neurocognitive impairment among those with HIV infection and to determine specific ART factors that may be linked to neurocognitive deficits without ignoring potential confounders to the development of HAND such as age, level of education, WHO clinical staging and presence of chronic illness.

Materials and Methods

Study design and setting
This was a cross-sectional analytical study which was conducted at Muhimbili National Hospital (MNH), a National Referral and Teaching Hospital with more than 1,500 bed capacity, with 1,000 - 1,200 outpatients per day (19). The hospital is located in Dar es Salaam, a major city in Tanzania with a population of about 4,364,541 as per the 2012 census (20). MNH also runs a CTC clinic from Monday to Friday with approximately, 100 patients attending per day.

Sample size and sampling procedure
A sample size of 328 was calculated using the Kish Leslie formula. Systematic sampling procedure was observed whereby every fifth participant from the attendance list was directed for interview once the inclusion and exclusion criteria were applied.

Inclusion/exclusion criteria
Patients included in the study were 18 years or older, able to give informed consent and fluent in either Swahili or English. Those with significant hearing or visual impairments, impaired articulation or limb disabilities (and unable to perform neurocognitive tasks) were excluded. However no patient in our sample met exclusion criteria.

Data collection and analysis

It took 45 working days to conduct the interview and assess 351 patients between July – August 2012. A total of 358 patients were recruited but seven of them were lost to follow-up. These patients were not included in the analysis. A questionnaire was used to determine socio-demographic and clinical profiles of participants. Socio-demographic characteristics included age, gender, years of formal education and duration of illness in years.

Clinical profile included WHO HIV clinical staging, and presence of chronic illness. A list of potential confounding illnesses such as diabetes, any cardiovascular diseases, epilepsy, malignancies, asthma, peptic ulcer diseases, sickle cell anemia, chronic kidney disease and other illnesses were recorded. Information on the patient's current regimen was also recorded, including proposed ability to penetrate the central nervous system based on CPE scoring system version 2010.

In CPE scoring system, an individual ART is given a score based on its ability to reach the CNS (22). Adding the scores of each individual ART in a combined regimen gives the sum of the CPE score for a given ART combination (see Table 1).

Table 1. Central Nervous System Penetration-Effectiveness Ranking

Drug Class	CPE Score			
	4	3	2	1
Nucleoside Reverse Transcriptase Inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenafovir Zalcitabine
Nonnucleoside Reverse Transcriptase Inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease Inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Strand Transfer Inhibitors		Raltegravir		

CPE indicates central nervous system penetration effectiveness: /r, ritonavir-boosted. Larger
CPE scores reflect estimates of better penetration or effectiveness in the central nervous system (eg. A ranking of 4 indicates the best penetration or effectiveness.

Neurocognitive function was determined using the International HIV Dementia Scale (IHDS) at a cut off point of 10 /12. This tool assesses memory recall, motor speed and psychomotor speeds as domains of neucognitive functions. This screening tool has a good pooled sensitivity of 0.90 [95% confidence interval (CI), 0.88–0.91] and overall specificity of 0.96 (95% CI, 0.95–0.97) under summary receiver operation (23).
Data was analyzed using Statistical Package for Social Science (SPSS) version 18. Factors associated with positive screening for neurocognitive deficits were determined using Chi-squared tests and Fisher's exact tests for cells with

observations less than five. Those with p-value of ≤ 0.05 were further analyzed under multivariate logistic regression.

Ethical consideration

The study obtained ethical clearance from the Muhimbili University of Health and Allied Science research clearance committee. The University uses Muhimbili National Hospital as a teaching hospital where the study was undertaken.

Results

Socio-demographic and clinical profile

Out of 351 participants, 240 (68.4%) screened positive for HIV-associated neurocognitive deficits. Seventy-eight out of 351 (22.3%), 149 (42.5%), 89 (25.4%), 35(10%) was aged between 18-35, 36-45, 46-55 and above 55 years, respectively. Females comprised 260/351 of the study participants (74%). Majority of participant attained less than seven years of formal education while for duration of illness majority had duration of illness of 1-5 years.

Patients were also categorized based on WHO clinical staging. 15.4% of participants fell into clinical stage I, 68.9% were in stage II, 12.5% were on stage III and 3.1% fell into stage IV. Only 59 (16.8%) participants had another chronic illness in addition to HIV/AIDS, with diabetes and cardiovascular disease making up 49.2% among those with chronic illnesses (see Table 2).

Table 2. SOCIO-DEMOGRAPHIC AND CLINICAL PROFILE

VARIABLE	CATEGORY	COUNT(N)	PERCENTAGE (%)
Age of patients (in years)	18-25	8	2.3
	26-35	70	19.9
	36-45	149	42.5
	46-55	89	25.4
	55+	35	10.0
Gender	Male	91	25.9
	Female	260	74.1
Years of formal education attained	≤ 7	211	60.1
	7-10	107	30.5
	>10	33	9.4
Duration in years since the first diagnosis	<1	29	8.3
	1-5yrs	162	46.2
	5-10yrs	121	34.5
	10+	39	11.1
WHO clinical staging	Stage I	54	15.4
	Stage II	241	68.9
	Stage III	44	12.6
	Stage IV	11	3.1
Presence of chronic illness	No	292	83.2
	Yes	59	16.8
Patient on ARTs	Yes	315	90
	No	36	10
CPE score category	≤ 7	97	30.7
	>7	218	69.3

Of all 351 patients, 315 (90%) were on ART and among these 218 (69.2%) were on ART combination with Central Nervous System penetration effectiveness (CPE) score of more than 7. The most common ART combinations used included AZT/3TC/EFV (31.7%), (d4T/3TC/NVP) (15.2%), d4T/3TC/EFV (10.8%) and AZT/3TC/NVP (10.2%). The single most common ART used was Lamivudine (3TC), with 276 (87.6%) of participants being on a 3TC-containing combination (Table 4).

Neurocognitive performance and associated factors

The mean score of neurocognitive performance based on IHDS was 9.35 with the median of 10, standard deviation of 1.89, ranging from minimal score of 2 to maximum score of 12. A greater proportion 26/36 (72.2%) of those who were not on ARVs had neurocognitive impairment compared to 214/315 (67.9%). However this was not statistically significant with p-value of 0.707 (Table 4).

One hundred eighty one (69.6%) of females screened positive for neurocognitive deficits compared to 59 (64.8%) of males, although this was not statistically significant at (P=0.390) (see Table 3.)

On descriptive analysis, we found that age and years of formal education were significantly associated with HAND with p values of 0.03 and 0.038, respectively. Other factors such as gender (p=0.39), number of years living with HIV since diagnosis (p=0.153), WHO clinical staging (p=0.08), presence of chronic illness (p=0.28) and being on ART (p=0.707) were not statistically significant, (see Table 3).

Table 3. Socio-demographic/clinical profile versus HAND

Variable		HIV-associated neurocognitive deficits [HAND]				P value
		Positive screening		Negative screening		
		N	%	N	%	
Age of patients	18-25	4	50.0%	4	50.0%	0.030
	26-35	43	61.4%	27	38.6%	
	36-45	95	63.8%	54	36.2%	
	46-55	66	74.2%	23	25.8%	
	55+	32	91.4%	3	8.6%	
Gender	Male	59	64.8%	32	35.2%	
	Female	181	69.6%	79	30.4%	0.390
Years of formal education	</= 7	153	72.5%	57	27.5%	
	7-10	63	58.9%	44	41.1%	0.038
	>12	23	69.7	10	30.3	
Duration in years since diagnosis	<1	25	86.2%	4	13.8%	
	1-5yrs	108	66.7%	54	33.3%	0.153
	5-10yrs	82	67.8%	39	32.2%	
	10+	25	64.1%	14	35.9%	
Clinical staging	I	28	52.8%	25	47.2%	
	II	166	68.9%	75	31.1%	0.080
	III	37	82.2%	8	17.8%	
	IV	9	75.0%	3	25.0%	
Presence of chronic illness	No	196	67.1%	96	32.9%	
	Yes	44	74.6%	15	25.4%	0.280

ARVs were categorized based on their CPE scores (22), those with a score above seven and those with a score seven or below. Of all 315 patients that were on ARV, a greater proportion 218(69.3%) used ARTs regimens with a score of above seven, while the rest had a score of seven or less. Of those who used

ARVs with a CPE score of less than seven, 76 (78%) screened positive for HAND compared to 135 (62%) of those who used ARV combination with CPE score of more than 7; this was statistically (p-value of <0.001).
The association of an individual antiretroviral drug within a particular combination was analyzed. Among the most common antiretroviral used, only efavirenz was significantly associated with neurocognitive impairment at P=0.039 while other antiretroviral drugs did not show significant association with neurocognitive impairment (see table 4).

Table 4. Association between ARV and HAND

Variable			HIV-ASSOCIATED NEUROCOGNITIVE DEFICITS				P value
			Positive screening		Negative screening		
			N	%	N	%	
PATIENT ON ARV		Yes	214	67.9%	101	32.1%	0.707
		No	26	72.2%	12%	27.8%	
CPE SCORE CATEGORY		≤ 7	76	78%	23	22%	<0.001
		>7	135	62%	83	38%	
ART TYPE	EFV	NO	53	62.3%	33	37.7%	0.039
		YES	168	73.4%	61	26.6%	
	3TC	NO	22	58.3%	17	41.7%	0.063
		YES	175	63.5%	101	36.5%	
	NVP	NO	130	56.4%	102	43.6%	0.170
		YES	53	64.1%	30	45.9%	
	d4T	NO	163	69.8%	70	40.2%	0.124
		YES	43	52.1%	57	47.9%	
	AZT	NO	40	30.2%	92	69.8%	0.339
		YES	71	38.8%	112	62.2%	

Under multivariate analysis we found that the use of ARV combination with CPE score of ≥7 was positively associated with HAND (p=0.02, OR=0.449 and C.I=0.27-0.748). We also found that having attained between seven to ten years of formal education was protective against HAND when computed against those who attained no formal education or had less than seven years of formal education (p=0.029, OR=1.129, C.I=0.444-2.874). Other variables such as age and use of efavirenz containing regimen showed no significant association on multivariate regression analysis. (Table 5).

TABLE 5. MILTIVARIATE REGERSSION ANALYSIS

Variable		STATISTICS			
		P value	Odds ratio	Confidence interval	
				Lower	Upper
CPE score		.02	0.449	.270	.748
Efv Usage		.119	1.490	.902	2.461
Years of Formal	0-7	Reference			
Education	7-10	.029	0.555	.327	.941
	10+	.798	1.129	.444	2.874
Age		.869	0.998	.973	1.024

Discussion

The aim of this study was to determine the relationship between ART regimens and neurocognitive functions among PLWHA.

Just like in previous studies, this study suggests that females are at higher risk of developing neurocognitive deficits (24)(16), contrary to reports that refute the link between gender and HAND (17-18).

This study shows that duration of formal education positively influence cognitive performances as report by few other studies(26) and usually those with more years of formal education to have much higher neurocognitive performance at least at baseline(27).

Both descriptive and multivariate analysis suggests high CPE was positively associated with better neurocognitive outcome. This supports the hypothesis that regimens with a high CPE score may be effective against CNS complications including HAND (7)(28)20) by directly inhibiting viral replications in the CNS (11). This also alludes to the idea that antiretroviral regimens with higher CPE score tend to improve overall survival and reduce incidence of CNS disease that may manifest as HAND (28).

Our findings agree with the theory that ARV drugs with higher CPE scores tend to lower both plasma and CSF viral concentrations to undetectable levels, more so than those with lower CPE scores (11)(14). In doing so they halt the pathogenic cascade induced by the virus, thus mitigating the HIV viral effect in the CNS including development of HAND(12).

This study evaluated the potential of the most frequently used cART in our study which included nevirapine, zidovudine, stavudine, efavirenz and lamivudine, In our case only efavirenz was found to be significantly associated with HAND under descriptive analysis. Overall efficacy of efavirenz is undisputed but it cannot be ignored that many neuropsychiatric and neurological complications of efavirenz (including HAND) have been demonstrated, though the mechanism is still unclear but growing evidence points to disturbances in brain mitochondrial function and bioenergetics(30-33).

Though efavirenz has been the ARV drug that has been documented as being associated with neurotoxicity(16)(25), other ARVs such as zidovudine have also been associated with CNS toxicity, manifesting as mania and psychosis, and stavudine association with peripheral neuropathy has also been implicated. Lamivudine at p-value of 0.063 was closest to statistical significance, this may be due to the fact that majority of the patients that were on lamivudine were also on efavirenz, which is well documented for its negative effect on cognitive functions. This means that what appears to be a correlation between lamivudine and HAND may actually be the default effect of nevirapine being paired with efavirenz.

In this study, although the trend suggested use of zidovudine to be a risk factor for cognitive impairment (Table 4), this was not statistically significant, one probable explanation may be the potential of AZT to cause psychiatric symptoms such as depression, that can mimic neurocognitive impairment but yet not enough to show true neurocognitive impairment as reflected in our study.

Despite providing many information on the correlation between neurocognitive deficits and ARV characteristics, this study was limited as it did not provide information on CD4 count and viral load which may indicate overall ART response.

There was no account given on psychiatric symptoms such as depression and anxiety symptoms that may have additive effect on poor neurocognitive performance.

Conclusion

The current opinion of the authors is in favor of using ARV with high CPE score while keeping in mind the potential for neurotoxicity

The study highlights the link between the use ARV and their association with HAND. However it is still not clear which combinations work best for each individual.

List of abbreviation

ABC – Abacavir
AIDS-Acquired immunodeficiency syndrome
ART-Anti retroviral therapy
ARV- Anti retroviral
AZT-Zidovudine
CPE-Central nervous system penetration effectiveness
d4T- Stavudine
ddI-Didanosine
3TC- Lamivudine
EFV- Efavirenz
FTC- Emtricitabine
HAND- HIV associated neurocognitive deficits
HIV- Human Immunodeficiency virus

IHDS- International HIV dementia scale
LPV- Lopinavir
NCDs- Neurocognitive deficits
NCI- Neurocognitive impairment
NVP- Navirapine
PLWH(A)- people living with HIV(AIDS)
TDF- Tenofovir
WHO- World Health Organization

Competing interest

The authors declare that they have no competing interest

Authors' contribution

AN is the main author, he conceived and designed the study and wrote the proposal for the study. DN, CO and AMM all supervised the study from the very beginning of the process, they all reviewed the manuscript and provided intellectual inputs. DN ensured that AN gets permission to use standardized tools for this research.

Acknowledgement

Special thanks go to Professor Silvia Kaaya of Muhimbili University of health and Allied Science for her intellectual input and advice, Dr. Praxeda Swai, Dr Mwajuma Mustapha, Dr Charles Obeid and the late Dr Sheka Joseph Sheka for all their help.
My wife and other family members for their endless support.
Lastly but not least I send my sincere gratitude to the patients who made this work worth doing.

References

1. Gulick RM. Antiretroviral Treatment 2010: Progress and Controversies. J Acquir Immune Defic Syndr 1999. 2010 Dec 1;55(Suppl 1):S43–8.

2. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. J Neurovirol. 2011 Feb;17(1):3–16.

3. Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010 Dec 7;75(23):2087–96.

4. Elbirt D, Mahlab-Guri K, Bezalel-Rosenberg S, Gill H, Attali M, Asher I. HIV-associated neurocognitive disorders (HAND). Isr Med Assoc J IMAJ. 2015 Jan;17(1):54–9.

5. Seggane Musisi EK, editor. Psychiatric Problems of HIV/AIDS and their management in Africa. Kampala-Uganda: Fountain Publishers; 2009.

6. Lawler K, Mosepele M, Ratcliffe S, Seloilwe E, Steele K, Nthobatsang R, et al. Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study. J Int AIDS Soc. 2010;13:15.

7. Liner KJ, Ro MJ, Robertson KR. HIV, antiretroviral therapies, and the brain. Curr HIV/AIDS Rep. 2010 May;7(2):85–91.

8. Letendre SL, Ellis RJ, Ances BM, McCutchan JA. Neurologic complications of HIV disease and their treatment. Top HIV Med Publ Int AIDS Soc USA. 2010 May;18(2):45–55.

9. Smurzynski M, Wu K, Letendre S, Robertson K, Bosch RJ, Clifford DB, et al. Effects of Central Nervous System Antiretroviral Penetration on Cognitive Functioning in the ALLRT Cohort. AIDS Lond Engl. 2011 Jan 28;25(3):357–65.

10. Tan IL, McArthur JC. HIV-associated neurological disorders: a guide to pharmacotherapy. CNS Drugs. 2012 Feb 1;26(2):123–34.

11. Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol. 2008 Jan;65(1):65–70.

12. Hong S, Banks WA. Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. Brain Behav Immun. 2015 Mar;45:1–12.

13. Spudich S, González-Scarano F. HIV-1-Related Central Nervous System Disease: Current Issues in Pathogenesis, Diagnosis, and Treatment. Cold Spring Harb Perspect Med [Internet]. 2012 Jun [cited 2015 Aug 18];2(6). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3367536/

14. Eisfeld C, Reichelt D, Evers S, Husstedt I. CSF penetration by antiretroviral drugs. CNS Drugs. 2013 Jan;27(1):31–55.

15. Decloedt EH, Rosenkranz B, Maartens G, Joska J. Central nervous system penetration of antiretroviral drugs: pharmacokinetic, pharmacodynamic and pharmacogenomic considerations. Clin Pharmacokinet. 2015 Jun;54(6):581–98.

16. Wright E. Neurocognitive impairment and neuroCART. Curr Opin HIV AIDS. 2011 Jul;6(4):303–8.

17. Akay C, Cooper M, Odeleye A, Jensen BK, White MG, Vassoler F, et al. Antiretroviral drugs induce oxidative stress and neuronal damage in the central nervous system. J Neurovirol. 2014 Feb;20(1):39–53.

18. Home - MUHIMBILI NATIONAL HOSPITAL [Internet]. [cited 2015 Sep 23]. Available from: http://www.mnh.or.tz/

19. Dar es Salaam. In: Wikipedia, the free encyclopedia [Internet]. 2015 [cited 2015 Sep 26]. Available from: https://en.wikipedia.org/w/index.php?title=Dar_es_Salaam&oldid=680085549

20. Antiretroviral CNS Penetration-Effectiveness (CPE) 2010 ranking predicts CSF viral suppression only in patients with undetectable HIV-1 RNA in plasma [Internet]. [cited 2015 Aug 23]. Available from: http://www.natap.org/2011/CROI/croi_139.htm

21. HU X, ZHOU Y, LONG J, FENG Q, WANG R, SU L, et al. Diagnostic accuracy of the International HIV Dementia Scale and HIV Dementia Scale: A meta-analysis. Exp Ther Med. 2012 Oct;4(4):665–8.

22. Hestad KA, Menon JA, Silalukey-Ngoma M, Franklin DR, Imasiku ML, Kalima K, et al. Sex differences in neuropsychological performance as an effect of human immunodeficiency virus infection: a pilot study in Zambia, Africa. J Nerv Ment Dis. 2012 Apr;200(4):336–42.

23. Morlat P, Parneix P, Douard D, Lacoste D, Dupon M, Chêne G, et al. Women and HIV infection: a cohort study of 483 HIV-infected women in Bordeaux, France, 1985-1991. The Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. AIDS Lond Engl. 1992 Oct;6(10):1187–93.

24. Marder K, Liu X, Stern Y, Malouf R, Dooneief G, Bell K, et al. Risk of human immunodeficiency virus type 1-related neurologic disease in a cohort of intravenous drug users. Arch Neurol. 1995 Dec;52(12):1174–82.

25. Bouwman FH, Skolasky RL, Hes D, Selnes OA, Glass JD, Nance-Sproson TE, et al. Variable progression of HIV-associated dementia. Neurology. 1998 Jun;50(6):1814–20.

26. Ritchie SJ, Bates TC, Deary IJ. Is Education Associated With Improvements in General Cognitive Ability, or in Specific Skills? Dev Psychol. 2015 May;51(5):573–82.

27. Gottesman RF, Rawlings AM, Sharrett AR, Albert M, Alonso A, Bandeen-Roche K, et al. Impact of Differential Attrition on the Association of Education With Cognitive Change Over 20 Years of Follow-up. Am J Epidemiol. 2014 Apr 15;179(8):956–66.

28. Garvey L, Winston A, Walsh J, Post F, Porter K, Gazzard B, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. Neurology. 2011 Feb 22;76(8):693–700.

29. Obiabo YO, Ogunrin OA, Ogun AS. Effects of highly active antiretroviral therapy on cognitive functions in severely immune-compromised HIV-seropositive patients. J Neurol Sci. 2012 Feb 15;313(1-2):115–22.

30. Funes HA, Apostolova N, Alegre F, Blas-Garcia A, Alvarez A, Marti-Cabrera M, et al. Neuronal bioenergetics and acute mitochondrial dysfunction: a clue to understanding the central nervous system side effects of efavirenz. J Infect Dis. 2014 Nov 1;210(9):1385-95.

31. Vigliano P, Boffi P, Bonassi E, Gandione M, Marotta C, Rainò E, et al. Neurophysiologic exploration: a reliable tool in HIV-1 encephalopathy diagnosis in children. Panminerva Med. 2000 Dec;42(4):267-72.

32. Funes HA, Blas-Garcia A, Esplugues JV, Apostolova N. Efavirenz alters mitochondrial respiratory function in cultured neuron and glial cell lines. J Antimicrob Chemother. 2015 Aug;70(8):2249-54.

33. Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV. Efavirenz and the CNS: what we already know and questions that need to be answered. J Antimicrob Chemother. 2015 Jul 22;

34. Caniglia EC, Cain LE, Justice A, Tate J, Logan R, Sabin C, et al. Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. Neurology. 2014 Jul 8;83(2):134-41.