

## HIV-1 INFECTION AMONG LATE DIAGNOSED PATIENTS ACCESSING ANTIRETROVIRAL THERAPY IN JOS, NIGERIA

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### ABSTRACT

Early diagnosis and estimation of duration of HIV-1 infection among the population is critical for public health intervention services in order to reduce risk associated with spreading of the virus. Over the years, reliable methods have been developed for estimating duration, and to differentiate early from late acquired HIV-1 infection. The cross-sectional study was carried out with newly enrolled patients at HIV treatment Centre of the Jos University Teaching Hospital. Avidity assay, viral load, CD4 cell count and WHO disease staging were used to characterize the patients. We described the socio-demographic, clinical and laboratory features of the study population. Of 230 patients, 90% had late and 10% early infection. The median age of the patients was 35 years, while the majority of the patients were female (64%). Median CD4<sup>+</sup> cell count was significantly lower in those lately diagnosed (131 cell/mm<sup>3</sup>). Pulmonary tuberculosis (PTB) co-infected patients comprised 12%, 20% of oropharyngeal candidiasis, 25% of chronic diarrhea, and 59% had WHO clinical stage 3 or 4. In conclusion, late diagnosis is the most common presentation to tertiary healthcare facility, though this pattern is changing as a result of scale-up antiretroviral treatment. The analysis showed that HIV viral load, CD4<sup>+</sup> cell counts, pulmonary tuberculosis co-infection and oropharyngeal candidiasis were significantly associated with late diagnosis of HIV infection. Therefore, there is need to intensify the present efforts on early routine HIV counseling and make ARVs available in all primary healthcare facilities in rural communities. This could reduce the frequency of late HIV diagnosis at tertiary institutions in order to avert AIDS condition.

### INTRODUCTION

Early diagnosis of HIV-1 infected individuals among the population is critical for public health intervention services in order to reduce risk associated with spreading of the virus. Over the past years reliable methods have been developed for estimating duration, and to differentiate recently (early) acquired from long-established (late) HIV-1 infection (Janssen *et al.*, 1998; Guy *et al.*, 2009). Classification of individuals as either recent from long-established (late) is based on; the increase in antibody avidity and or antibody titer level (Rawal *et al.*, 2003; Barin *et al.*, 2005). However, the introduction of combined

antiretroviral therapy (cART) has proved effective in treatment and care of HIV infection, and has led to significant reductions in morbidity and mortality (Palella *et al.*, 1998). Although the optimal time at which to initiate therapy remains controversial around the world (Levy, 1998), but it should be noted that early presentation is key to avoid onset of emergence of AIDS defining illnesses. Early diagnosis of HIV infection means timely access to treatment initiation to ensure maximum benefit and may serve to bring about drastic reduction in HIV-1 progression and transmission even among people of risky behaviors (Weinhardt *et al.*, 1999). HIV infection usually precedes low CD4

cell count and emergence of the AIDS defining illnesses and the appearance of any of the illnesses in those unaware of having HIV infection is considered to be a failure in the use of early diagnosis strategy. Late diagnosis in the course of HIV infection accounts for incidence of some AIDS defining cases which is as result of late presentation for treatment and care (Girardi *et al.*, 2000; Valdiserri *et al.*, 1999). Other causes of AIDS defining incidence among those on drug are poor adherence (Chesney *et al.*, 1999) and emergence of resistance mutations to antiretroviral drugs for maximum therapeutic influence (Pe´rez Alvarez *et al.*, 2000; Puig *et al.*, 2000).

Late diagnosis which reflects late presentation or late entry into care has consequences for the individual in terms of poorer treatment outcomes (Battegay *et al.*, 2007; Lanoy *et al.*, 2007), and for the general population in terms of the risk of transmission due to high viral load (Quinn *et al.*, 2000). It must be emphasized that late presentation amongst others has economic impact such as high management cost following few months of presentation (Fleishman *et al.*, 2010). The barriers to patients early testing includes; concerns about the impact of a positive result, fears of lack of confidentiality, stigmatization and limited knowledge about accessing treatment (Deblonde *et al.*, 2010). There are also documented concerns by health providers; such as worry about informing individuals of a HIV-positive test result, language barriers, issues around lengthy counseling and time wasting, and poor knowledge about HIV infection and avoidable risk behaviors (Yazdanpanah *et al.*, 2010).

Our earlier study (Anejo-Okopi *et al.*, 2014) on smaller sample size presented data on long-standing HIV-infection using antibodies avidity measurement and many other reported studies within and outside the country applied various definitions for late presentations (Alvarez-Uria *et al.*, 2012; Althoff *et al.*, 2010; Kitahata *et al.*, 2009), but data from North Central Nigeria are particularly scarce, therefore a much larger sample size is needed to determine duration of HIV-1 infection of late diagnosed and

associated characteristics using demographic, laboratory and clinical markers in the descriptions to help inform the populace, health providers and decision makers on the way forward for nation-wide HIV testing strategies. This will provide a platform for future monitoring of late diagnosis and effects on presentation for care following appropriate interventions. The importance of timely access to HIV services, including testing, linkage to treatment and continued retention in care is increasingly recognized at both the individual and population levels (Gardner *et al.*, 2011; Girardi *et al.*, 2007). Specifically, studies have shown that late presentation (LP) to HIV care services has severe consequences for the morbidity and mortality of individuals living with HIV and can also increase the risk of transmission to others (Cohen *et al.*, 2011). The aim of the present study is to describe characteristics associated with duration of HIV infection in late diagnosed HIV-infected patients accessing cART

## MATERIALS AND METHODS

### Study Setting

The cross-sectional study was carried out at the HIV treatment Centre of the Jos University Teaching Hospital (JUTH) in collaboration with AIDS Prevention Initiative in Nigeria (APIN) program. This clinic provides comprehensive HIV care services for the city of Jos and its environs. Since 2004, the clinic has been supported by the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR). All HIV-related clinic data for enrolled patients are maintained in electronic databases. Laboratory bench work for avidity assay was carried out at CDC supported HIV-Research Laboratory, Kenya Medical Research Institute, Kisumu, Kenya.

### Study Design and Population

The study participants were prospectively enrolled patients, aged 18 years and above, diagnosed as HIV-1 positive at the adult HIV clinic of JUTH and were prequalified to commence cART. The enrollment was from October, 2010 and April, 2011. All patients included in the study provided written informed

consent for the use of their data for research as approved by the institutional review boards at the Jos University Teaching Hospital. The use of secondary data was approved by Harvard School of Public Health. An electronic database (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA) for patients' demographic, clinical, laboratory data was designed by the Harvard PEPFAR/APIN program and utilized in the clinic. The patients included in this analysis were those who attended the clinic for the first time and have been recently diagnosed with HIV-infection and classified as recent (Early) infection and long standing (Late) Infection) using avidity assay and their CD4<sup>+</sup> T cells measurement at the point of enrollment. All patients HIV status was confirmed by double rapid test and indeterminate result by tiebreaker and western blot.

### Definitions and Measurements

HIV-1 infection was diagnosed and classified as early and late infection using the avidity assay (Suligoi, *et al.*, 2003; Anejo-okopi *et al.*, 2014). We also used WHO stage at enrollment (WHO, 2005). The WHO HIV infection staging system applies clinical condition to measure disease progression and is widely used in resource-limited settings including Nigeria. The staging system has been shown to reliably predict survival times or disease progression (Teck *et al.*, 2005; Kigozi *et al.*, 2009). We categorized WHO stage as not severe (stages 1 and 2) or severe (stages 3 and 4). The patients also had their CD4<sup>+</sup> cell count measured and those with CD4<sup>+</sup> <200 cell/mm<sup>3</sup> were considered to be late testers, while those with  $\geq 200$  cell/mm<sup>3</sup> but without AIDS defining condition at diagnosis were also regarded as early tester. We also used clinical variables such as; hepatitis B virus (HBV) status, pulmonary tuberculosis (PTB), oropharyngeal candidiasis, chronic diarrhea and Kaposi sarcoma. The study also utilized data that were captured using standardized questionnaire including demographic variables; age, sex, marital status, occupation, state of residence, mode of transmission, partner status and spouse ARV treatment status.

Late diagnosis and/or long standing infection was defined as a person diagnosed with HIV with a CD4 count below 200mm<sup>3</sup> or an AIDS defining event regardless of the CD4<sup>+</sup> cell count, and with serum samples having an avidity index of >0.80 while those with an avidity index of  $\leq 0.80$  were classified as early and/or recent infection. All persons were required to have avidity index test, CD4 cell count and viral load measured at baseline following diagnosis. Kaposi's sarcoma was diagnosed based on clinical features (WHO, 2007).

### Laboratory Methods

Laboratory tests carried out were part of the existing HIV treatment programme. Two different rapid HIV tests: Uni-Gold (Trinity Biotech Plc Bray Co Wicklow, Ireland) and Determine HIV-1/2 test (Determine Alere Medical Co., Ltd 357 Matsuhidai, Japan) were used for HIV sero-diagnosis. Flow cytometry (Partec GmbH, Munster Germany) was used to determine the CD4<sup>+</sup> lymphocyte count and Roche Cobas Amplicor HIV-1 Monitor, version 1.5 (Roche Diagnostics GmbH, Mannheim, Germany) was used to determine HIV-1 RNA viral load. Enzyme immunoassay (EIA) (Monolisa HBsAg Ultra3; Bio-Rad) was used to determine the HBsAg. Patients were not screened for hepatitis C virus (HCV).

The estimation of duration of HIV infection was carried out using the IgG Avidity Index (AI) test involving automated anti-HIV enzyme immunoassay (EIA) as previously described (Anejo-okopi *et al.*, 2014). The method was based on the rationale that antibodies produced in early phase of an infection show a low avidity increase progressively with time after exposure to immunogens. Thus, the low avidity indicates a recent infection and this was based on previous reports that a cut-off of 0.80 for the AI correspond to mean sero-conversion duration of 180 days using AXSYM HIV1/2gO. Serum samples with an AI of  $\leq 0.80$  were classified as "recent infection", and those with an AI of >0.80 were classified as "established infection" (long-standing infection). Each of the samples stored at -80°C were thawed, and two aliquots

of 0.2µl each were subjected to a pre-analytic dilution with phosphate-buffered (1:10) saline. After incubation at room temperature for 5 minutes, the aliquots were assayed using the automated AXSYM HIV1/2gO assay (Abbott Diagnostics Division, Delkenheim, Germany) without modifying the recommended protocol by the manufacturer, and the AI results were obtained for each specimen. All specimens were tested in parallel under routine conditions.

### Statistical analysis

The results were analyzed using EPI Info statistical software version 7.1.1.14 (CDC, Atlanta Georgia, USA). Results were summarized in frequencies and proportions for categorical variable, while continuous variables, depending on distribution, were summarized by mean or median. For the purpose of analysis the following variables were categorized: age, WHO clinical stage, viral load and CD4 cell count. WHO clinical stage (stage 3 or 4 versus stages 1 or 2) was based on clinical severity (WHO, 2005), while HIV RNA viral load ( $<4.6$  log<sub>10</sub> versus  $\geq 4.6$  log<sub>10</sub> copies/ml) was obtained using the median cut-off value. The outcome variable defined as late infection was obtained using the avidity assay result cut-off level  $P > 0.08$  which is regarded as long established infection (Suligo *et al.*, 2003), levels of significance were set at  $P < 0.05$ . All other variables were considered as independent variables. The bivariate analysis using Chi squared test or Fisher's exact test was used to determine associations of each independent variable with duration of HIV infection

### RESULTS

The median age of the patients was 36 years, while the majority of the patients were female (64%) and male was 36%. The main mode of HIV transmission was by heterosexual sex (85%). Majority of the patients were either single or separated (81%), most patients lived in Plateau State (65%), majority of patients had secondary education and above (70%). Majority of the patients were unemployed (44%), 32% employed, and students 17%. Interestingly most patients do not know about the treatment status of their spouses (90%), and those who consume

alcohol were diagnosed late (70%) with  $P = 0.08$  (Table 1).

The patients who knew HIV positive status of their spouses were 53%, and those whose spouses had HIV negative status were 47%. Of the 230 patients 94% tested negative for hepatitis B virus surface antigen (HBsAg), only 5.8% had hepatitis B virus infection (Table 1). About ninety (90%) of the patients had Late (established/long-standing) and 10% had Early (Recent) infection. The median RNA log of 230 subjects was 4.6 (IQR 4.1-4.9). The median CD4<sup>+</sup> cell count (131 cell/mm<sup>3</sup>) was significantly lower in those with lately diagnosed, IQR (67-251), while those that were diagnosed early had CD4<sup>+</sup> cell count of 372 cell/mm<sup>3</sup>, (IQR, 152-600). The analysis showed that HIV viral load, CD4<sup>+</sup> cell count had a significant association with late HIV-1 diagnosis (Table 2). In relation to pulmonary tuberculosis (PTB) co-infection, 12% had PTB infection. The frequency of oropharyngeal candidiasis was 20%, chronic diarrhea 25%, while majority of the patients did not have Kaposi sarcoma (95%). Interestingly 59% of the patients were WHO clinical stage 3 or 4. Pulmonary tuberculosis, oropharyngeal candidiasis, and WHO clinical stage 3 or 4 were also significantly associated to late HIV-1 infection  $p < 0.05$  (Table 3).

### DISCUSSION

In the last three decades since emergence of AIDS and introduction of combination therapy against the dreaded HIV, the scientific advances in the management of the disease and other associated infections have been seemingly substantial. The calculated and manageable risk-ratios are well tilted towards earlier initiation of treatment amongst those known to have been diagnosed and presented early. However, it's a well-known fact that late diagnosed individuals miss most benefits associated with early treatment and are faced with the negative consequences of late presentation with disease progression, high morbidity and mortality, while the health care systems are often burdened with stressed facility. Studies have shown that early

treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level (WHO, 2013). Late diagnosis at tertiary institutions appears common but with conflicting reasons at presentations. Although, the factors associated with late diagnosed HIV at presentation differ in different populations. It is generally more common among those who do not perceive, or did not perceive themselves at high risk of infection. In view of this, late presentation tends to be more common among male with heterosexual transmissions and few of an unknown mode of transmission as earlier reported by Kiwanuka *et al.* (2014) and Girardi *et al.* (2007). The role of heterosexual transmission as a major route of HIV-1 infection has been clearly supported with data from routine antenatal HIV testing in the national healthcare facilities (Sagay *et al.*, 2006).

Our finding showed that ninety percent (90%) of patients enrolled for cART were diagnosed with late with HIV-1 infection and only a few individuals presented for care had recent HIV-1 infection (10%). The male patients had higher rates of late diagnosed at presentation (63.5%) compared to females who were diagnosed early (73%) ( $P < 0.05$ ). This suggests that females have better understanding of risk of HIV-1 infection and are more aware of routine testing especially those who had attended antenatal clinics for prevention of mother to child transmission (Sagay *et al.*, 2006; Awoyemi *et al.*, 2011; Gesesew *et al.*, 2013). Other factors accounting for this disproportionality may be awareness of HIV-1 infection status and accompanied stigmatization. Similarly, women are known to be more willing to know their HIV status and to access care than men (Kigozi *et al.*, 2010; Kiwanuka *et al.*, 2014).

Another socio-economic factor found to be associated with late diagnosis and duration of infection was consumption of alcohol (70%). There was high proportion of frequency of those consuming alcohol although with no statistical significance ( $p=0.08$ ) and this is a confirmation of the role of alcohol consumption in

influencing behaviors negatively (Zachariah *et al.*, 2003; Kalichman *et al.*, 2007). At the operational level, HIV prevention strategies can be best implemented in alcohol serving establishments. This can be achieved by integrating HIV prevention into well-established and frequently attended social institutions, such as bars, beer halls and or alcohol drinking points, An earlier study reported that beer shops owners express interest in the possibility of implementing HIV prevention interventions in their businesses, suggesting that there is an opportunity for HIV prevention messages to be delivered more efficiently in alcohol serving businesses (Kalichman *et al.*, 2007). Condoms can be made available and accessible in drinking halls with minimal disruption to the environmental safety laws, and can be promoted with simple messages displayed in small media such as posters or brochures. Furthermore, HIV prevention efforts should focus on alcohol consumers because of its effect on behavioral patterns such as failure to use condom, denials that affect healthcare seeking which often result to late diagnosis. In order to be more effective, HIV/AIDS prevention strategies designed for high risk groups such as drug users must take into account the role of alcohol and understanding of the population diversities and complexities.

Our finding also observed high proportion of late diagnosed patients (65%) among those resident outside Plateau State compared to those who reside in Plateau (35%) with higher proportion of patients diagnosed early. This may be due to proximity of the health facility in both groups. Some studies have shown that late diagnosis was commoner and associated with low CD4 cell count ( $<200 \text{ cell/mm}^3$ ) and AIDS defining illnesses. Amongst other factors reported to affect poor clinical outcome on presentation were HIV viral load at baseline, distance of healthcare facility from community and antiretroviral initiation time (Girardi *et al.*, 2007, Ebonyi *et al.*, 2014, Crabtree-Ramirez *et al.*, 2012; Antinori *et al.*, 2011). It could be argued that patients residing in Plateau State were more likely to have early HIV diagnosis compared to those residing outside the state due

to closeness of the healthcare facility which has lesser financial implications.

Our finding showed that majority had CD4<sup>+</sup> cell count below 200 cell/mm<sup>3</sup>, and this had significant association to late diagnosis at

presentation ( $p < 0.05$ ). Similarly, we observed high frequency of those categorized as WHO stage 3 or 4 (57%) ( $P < 0.05$ ) with significant association to late diagnosis as it corroborates with our earlier study (Abaynew *et al.*, 2011; Ebonyi *et al.*, 2014; Agaba *et al.*, 2014).

Table 1. Characteristics of newly diagnosed HIV-1 infected patients at presentation to JUTH tertiary treatment center according to duration of infection

Characteristics	Time of Enrolment n= 230		P value
	Late 208(90.4% )	Early 22(9.6%)	
<b>Age (years) Category</b>			0.70
15 – 24	22(10.6)	3(13.6)	
25 – 34	98(47.1)	12(54.5)	
35 – 44	67(32.2)	3(13.6)	
45-54	13(6.2)	2(9.1)	
≥55	8(4.0)	2(9.1)	
Median (IQR)	36(31-60)	36(15-37)	0.26†
<b>Sex</b>			<b>0.02</b>
Male	132(63.5)	16(72.7)	
Female	76(36.5)	6(27.3)	
<b>State of Residence</b>			<b>0.06</b>
Plateau State	74(35.0)	16(72.7)	
Other States	134(65.0)	6(27.3)	
<b>Education level</b>			<b>0.56</b>
≤Primary	128(61.5)	10(45.5)	
≥Secondary	80(38.5)	12(54.5)	
<b>Occupation</b>			<b>0.56</b>
Student	15(17.0)	1(4.5)	
Unemployed	91(44.0)	3(13.6)	
Trading	35(17.0)	5(22.7)	
Employed	67(32.2)	13(59.1)	
<b>Alcohol consumption</b>			<b>0.08</b>
Yes	146(70.)	6(27.3)	
No	62(30.0)	14(64.0)	
<b>Marital Status</b>			<b>0.07</b>
Married	36(17.3)	8(36.4)	
Single/Separated	172(83.0)	14(63.6)	
<b>Mode of Transmission</b>			<b>0.85</b>
Heterosexual	180(86.5)	18(82.0)	
Transfusion	2(1.0)	3(14.0)	
Unknown	26(2.0)	0.0%	
<b>Treatment Awareness of Spouse on ART</b>			<b>0.37</b>
Yes	22(10.6)	1(4.5)	
No	186(89.4)	21(95.5)	
<b>HIV Partner Status</b>			<b>0.55</b>
Positive	109(52.4)	13(59.1)	
Negative	99(47.6)	9(41.0)	
<b>HBV co-infection</b>			<b>0.53</b>
Yes	12(5.8)	2(9.1)	
No	196(94.2)	20(90.9)	

Table 2. Laboratory markers of newly diagnosed HIV-1 infected patients at presentation to JUTH tertiary treatment center according to duration of infection

Characteristics	Time of Enrolment n= 230		P value
	Late 208(90.4% )	Early 22(9.6%)	
<b>Log RNA Viral Load copies/mL</b>			0.50
≤4.9	132(65.3)	16(72.7)	
>4.9	76(36.5)	6(27.3)	
Median (IQR)	4.8(4.3-5.0)	4.3(4.2-4.9)	<b>0.01†</b>
<b>CD4+ Grouping</b>			<b>0.03</b>
≥200	91(43.7)	15(68.0)	
<200	117(56.2)	7(32.0)	
Median (IQR)	131 (67-251)	372 (152-600)	<b>0.03†</b>

Table 3. Co-infections and Clinical characteristics of newly diagnosed HIV infected patients at presentation to JUTH tertiary treatment center according to duration of infection

Characteristics	Time of Enrolment n= 230		P value
	Late 208(90.4% )	Early 22(9.6%)	
<b>Pulmonary tuberculosis (PTB)</b>			<b>0.001</b>
Yes	26(12.5)	1(4.5)	
No	182(87.5)	21(95.5)	
<b>Oropharyngeal Candidiasis</b>			<b>0.035</b>
Yes	42(20.2)	3(13.6)	
No	166(79.8)	19(86.4)	
<b>Chronic Diarrhoea</b>			<b>0.06</b>
Yes	48(23.1)	9(40.9)	
No	160(76.9)	13(59.1)	
<b>Kaposi Sarcoma</b>			<b>0.07</b>
Yes	11(5.3)	1(4.5)	
No	197(94.7)	21(95.5)	
<b>WHO clinical Stages</b>			<b>0.001</b>
Stages 1 & 2	81(38.9)	6(27.3)	
Stages 3 & 4	119(57.2)	16(72.7)	

WHO stage 3 and 4 has been classified and defined as HIV infections with severe clinical symptoms that are known to be associated with low CD4<sup>+</sup> cell count like similar studies in Europe and African countries (Forbi *et al.*, 2010; Kigozi *et al.*, 2010; Ebonyi *et al.*, 2014). Furthermore, HBV and HIV share similar routes of transmission and patients with hepatitis infection should also be offered screening for HIV infection. It was observed that about 6% of the diagnosed patients had HBV infection but did not have significant association with late infection, though the treatment program gives dual activity drugs for everyone co-infected with HBV infection as recommended standard care. It is a well-documented fact that Hepatitis co-infection in HIV-infected patients has negative impact on treatment outcomes of cART

leading to high morbidity and mortality among these groups of patients (Battegay *et al.*, 2007; Idoko *et al.*, 2009).

Similarly, we also observed that 13% of patients reported unknown route of transmission and this may suggest high risk group who for some social reasons did not want to disclose their route of transmission for some perceived associated stigma. The need to embark on targeted awareness and expansion of voluntary counseling and testing services to wider sectors of population would solve speculative issues of exclusion with consequential reduction in delayed testing.

As expected, some patients who were diagnosed late had clinical conditions commonly

associated with late presenters, amongst these factors; pulmonary tuberculosis and oropharyngeal candidiasis had a significant association ( $p < 0.05$ ), while chronic diarrhea and Kaposi sarcoma ( $p = 0.07$ ) had no significant association, although, KS is an AIDS defining illness (WHO, 2007). The observed greater clinical severity which was significantly associated with late diagnosis were pulmonary tuberculosis and oropharyngeal candidiasis and this has been attributed to advance stages of the disease, and many of this category die shortly after being diagnosed or even before drug initiation (Kiwunuka *et al.*, 2014; Girardi *et al.*, 2007; Boulle *et al.*, 2014). However, in the recent past, the use of inpatient hospital resources by patients with HIV infection has reduced drastically due to decrease in morbidity associated with the use of cART (Mocroft *et al.*, 2004), but those diagnosed late now account for a high proportion of resource use and cost implications, particularly in the first few months of care after presentation (Badri *et al.*, 2006). It is on this premise that the greater potential role of cART in controlling the spread of the epidemic has now been placed on promoting earlier diagnosis of HIV infection (UNAIDS/WHO, 2004).

Our findings support the necessity of reconsidering the current national prevention strategies and expanding early access to voluntary counseling and testing to other subsets of the population not traditionally considered at risk or even to the general population in order to prevent the potential harmful consequences of late cART initiation. Also, there is the need to implement better strategies to have recently diagnosed patients enter into care in a smooth and expeditious manner. The Nigerian health system currently does encourage this transition because many centers do not embark on confirmation of HIV infection with Western Blot before initiating antiretroviral therapy. The implementation of policies similar to the CDC's recommendation of offering HIV-testing to all people 13-64 years of age in clinical care settings may contribute to this purpose (CDC, 2003). The implementation strategies of universal testing will no doubt improve the

clinical outcome of subjects receiving earlier cART treatment, and in a large scale prevent transmission of HIV (Kitahata *et al.*, 2009; Girardi *et al.*, 2007).

## CONCLUSION

In conclusion, in our center, late diagnosis is the most common presentation to tertiary healthcare facility, though this pattern is changing as a result of scale-up antiretroviral treatment. The independent variables associated with late diagnosis were age 25-34 years, sex, resident outside of plateau state, low level of education, unemployment, single or separated, marital status and use of alcohol. Other factors such as laboratory markers; high viral load, low CD4<sup>+</sup> cell counts were significantly associated with late diagnosis of HIV-1. There were also some clinical conditions known to be significant association to late diagnosis namely; pulmonary tuberculosis, oropharyngeal candidiasis and WHO stage 3 and 4. Although more research is needed to drive home the need and implications for delayed testing and access to treatment, however, recommendation to make testing readily available, affordable and unrestrictive access to treatment centers must be encouraged. There is the need to intensify the present efforts on early routine HIV counseling and make ARVs available in all primary healthcare facilities in rural communities to reduce the frequency of late HIV diagnosis resulting in poor clinical outcomes.

**Conflict of Interest:** the authors declared that there was no conflict of interest.

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## REFERENCES

- Abaynew, Y.1., Deribew, A. and Deribe, K. (2011). Factors associated with late presentation to HIV/AIDS care in South Wollo Zone Ethiopia: a case-control study. *AIDS Res Ther*, 8:(8):1-6.
- Agaba , A.P, Meloni, T. S., Sule, H. M., Agbaji, O.O., Ekeh, N.P., Job, G.C., Nyango, N., Ugoagwu, P.O., Imade, G.E., Idoko, J. A. and Kanki, J. P. (2014). Patients who present late to HIV care and associated risk factors in Nigeria. *HIV Med*, 10: 1-10.
- Althoff, N.K., Gange, J.S., Klein, B.M., Brooks, T.J., Hogg, S.R., Bosch, J.R., Horberg, A.M., Saag, S.M., Kitahata, M. M., Justice, C.A., Gebo, A.K., Eron, J. J., Rourke, B.S., John Gill, M., Rodriguez, B., Sterling, R. T., Calzavara, M. L., Deeks, G.S., Martin, N.J., Rachlis, R.A., Napravnik, S., Jacobson, P.L., Kirk, D.G., Collier, C. A., Benson, A. C., Silverberg, J.M., Kushel, M., Goedert, J. J., McKaig, G.R., Van Rompaey, E.S., Zhang, J., and Moore D.R. (2010). Late Presentation for HIV Care in the United States and Canada *Clin Infect Dis*, 50(11): 1512-1520.
- Alvarez-Uria, G., Midde, M., Pakam , R., Kannan, S., Bachu, L. and Naik, P. K. (2012)c. Factors associated with late presentation of HIV and estimation of antiretroviral treatment need according to CD4 lymphocyte count in a resource-limited setting: data from an HIV cohort study in India. *Interdisciplinary Perspect Infect Dis*, 10. (12) 293795-293797.
- Anejo-Okopi, J.A., Agbaji, O.O., Ebonyi, A. O., Agaba, P.A., Onywera, H., Oguche, S., Mbaawuaga, E.M., Audu, O., Abba, J.O., Nimzing, L., Isa, S.E., Olonitola, S.O., Idoko, J.A., Okonkwo, P. (2014). Factors associated with long-standing HIV-1 infection among HAART treatment-naïve adults in Jos, Nigeria. *International Journal of Microbiology and Application*, 1(1): 11-17
- Antinori, A., Coenen, T., Costagliola, D., Dedes, N., Ellefson, M., Gatell, J., Girardi, E., Johnson, M., Kirkm O., Lundgren, J., Mocroft, A., D'Arminio Monforte, A., Phillips, A., Raben, D., Rockstroh, J.K., Sabin, C., Sönnernborg, A. and De Wolf, F. (2011). Late presentation of HIV infection: a consensus definition. *HIV Med*. 12: 61-64.
- Awoyemi, T., Obayelu, A. and Opaluwa, I. (2011). Effect of distance on utilization of health care services in rural Kogi State, Nigeria. *J Hum Ecol*. 35(1):1-9
- Badri, M., Cleary, S., Maartens, G., Pitt, J., Bekker, L.G., Orrell, C. and Wood, R. (2006). When to initiate highly active antiretroviral therapy in sub-Saharan Africa? A South African cost effectiveness study. *Antivir Ther*, 11:63-72.
- Barin, F., Meyer, L., Lancar, R., Deveau, C., Gharib, M., Laporte, A., Desenclos, J.C. and Costagliola, D. (2005). Development and validation of an immunoassay for identification of recent HIV-1 infections and its use on dried serum spots. *J Clin Microbiol*, 43: 4441-4447.
- Battegay, M., Fluckiger, U., Hirschel, B., Furrer, H. (2007). Late presentation of HIV-infected individuals. *Antivir Ther*, 12: 841-851.
- Boulle, A., Schomaker, M., May, M.T., Hogg, R.S., Shepherd, B.E., Monge, S., Keiser, O., Lampe, F.C., Giddy, J., Ndirangu, J., Garone, D., Fox, M., Ingle, S.M., Reiss, P., Dabis, F., Costagliola, D., Castagna, A., Ehren, K., Campbell, C., Gill, M.J., Saag, M., Justice, A.C., Guest, J., Crane, H.M., Egger, M., Sterne, J.A (2014). Mortality in Patients with HIV-1 Infection Starting Antiretroviral Therapy in South Africa, Europe, or North America: A Collaborative Analysis of Prospective Studies. *PLoS Med*, 11(9): 1-14.
- Centers for Disease Control and Prevention. (CDC). (2003). Late versus early testing of

- HIV sites, United States, 2000-2003. *MMWR Morb Mortal Wkly Rep*; 32:581-586.
- Chesney, M. A., Ickovics, J., Hecht, F. M., Sikipa, G., Rabkin, J. (1999). Adherence: a necessity for successful HIV combination therapy. *AIDS*, 13(suppl A):S271-S278.
- Cohen, M.S., Chen, Y.Q., McCauley, M., Gamble, T., Hosseinipour, M.C., Kumarasamy, N., Hakim, J.G., Kumwenda, J., Grinsztejn, B., Pilotto, J.H., Godbole, S.V., Mehendale, S., Chariyalertsak, S., Santos, B.R., Mayer, K.H., Hoffman, I.F., Eshleman, S.H., Piwowar-Manning, E., Wang, L., Makhema, J., Mills, LA, de Bruyn, G., Sanne, I., Eron, J., Gallant, J., Havlir, D., Swindells, S., Ribaud, H., Elharrar, V. and Burns, D. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*, 365(6):493-505.
- Crabtree-Ramírez, B., Caro-Vega, Y., Belaunzarán-Zamudio, F., Sierra-Madero, J. (2012). High prevalence of late diagnosis of HIV in Mexico during the HAART era. *Salud Publica Mex*; 54:506-514.
- Deblonde, J., De Koker, P., Hamers, F.F., Fontaine, J., Luchters, S. and Temmerman M. (2010). Barriers to HIV testing in Europe: a systematic review. *Eur J Public Health*, 20: 422-432.
- Ebonyi1, O. A., Agbaji, O. O., Anejo-Okopi, A. J., Oguche, S., Agaba, A. P., Sagay, A.S., Okonkwo. P. (2014). Factors associated with a low CD4 count among HIV-1 Infected patients at enrolment into HAART in Jos, Nigeria, *British Journal of Medicine and Medical Research*, 4(13):1-10
- Fleishman, J. A., Yehia, B. R., Moore, R. D. and Gebo, K.A. (2010). The economic burden of late entry into medical care for patients with HIV infection. *Med Care*, 48: 1071-1079
- Forbi, C. J., Forbi, D.T., Agwale, M.S. (2010). Estimating the time period between infection and diagnosis based on CD4+ counts at first diagnosis among HIV-1 antiretroviral naïve patients in Nigeria. *J Infect Dev Ctries*, 4(10): 662-667.
- Gardner, E. M., McLees, M.P., Steiner, J.F., Del Rio, C., Burman, W.J. (2011). The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*, 52(6):793-800
- Gesesew, H. A., Tesfamichael, F. A., Adamu B.T. (2013). Factors Affecting Late Presentation for HIV/AIDS Care in Southwest Ethiopia: A Case Control Study. *Public Health Research*, 3(4):98-107
- Girardi, E., Sabin A.C., Monforte, A.A. (2007). Late Diagnosis of HIV Infection: Epidemiological Features, Consequences and Strategies to Encourage Earlier Testing *J Acquir Immune Defic Syndr*, 46: S3-S8.
- Girardi. E., Sampaolesi, A., Gentile M., Nurra, G., Ippolito, G. (2000). Increasing proportion of late diagnosis of HIV infection among patients with AIDS in Italy following introduction of combination antiretroviral therapy. *J Acquir Immune defic Syndr*, 25:71-76.
- Guy, R., Gold, J., Calleja, J.M., Kim, A.A., Parekh, B., Busch, M., Rehle, T., Hargrove, J., Remis, R.S. and Kaldor, J.M. (2009). Accuracy of serological assays for detection of recent infection with HIV and estimation of population incidence: a systematic review. *Lancet Infect Dis*, 9: 747-759.
- Idoko, J., Meloni, S., Muazu, M., Nimzing, L., Badung, B., Hawkins, C., Sankalé, J., Ekong, E., Murphy, R., Kanki, P. and Thio, L.C. (2009). Impact of hepatitis B virus infection on HIV response to antiretroviral therapy in Nigeria, *Clin Infect Dis*, (8): 1268-1273.

- Janssen, R/S/, Satten, G.A., Stramer, S.L., Rawal, B. D., O'Brien, T.R. (1998). New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *JAMA*, 280: 42-48.
- Kalichman, C.S, Simbayi C.L., Kaufman, M., Cain, D., Jooste, S. (2007). Alcohol Use and Sexual Risks for HIV/AIDS in Sub-Saharan Africa: Systematic Review of Empirical Findings *Prev Sci.* 8:141-151.
- Kigozi, M., Dobkin, M.L., Martin, N.J., Geng, H.E., Muyindike, W., Emenyonu, I. N., Bangsberg, R.D., and Hahn, A.J. (2009). Late disease stage at presentation to an HIV clinic in the era of free antiretroviral therapy in sub-Saharan Africa *J Acquir Immune Defic Syndr*, 52(2): 1-21.
- Kitahata, M.M., Gange, S.J., Abraham, A.G., Merriman, B., Saag, M.S., Justice, A.C., Hogg, R.S., Deeks, S.G., Eron, J.J., Brooks, J.T., Rourke, S.B., Gill. M.J., Bosch, R.J., Martin, J.N., Klein, M.B., Jacobson, L.P., Rodriguez, B., Sterling, T.R., Kirk, G.D., Napravnik, S., Rachlis, A.R., Calzavara, L.M., Horberg, M.A., Silverberg, M.J., Gebo, K.A., Goedert, J.J., Benson, C.A., Collier, A.C., Van Rompaey, S.E., Crane, H.M., McKaig, R.G., Lau, B., Freeman, A.M., Moore, R.D. (2009). Effect of early versus deferred ART for HIV on survival. *N Engl J Med*, 360(18):1815-1826.
- Kiwanuka, N., Ssetaala, A., Nalutaaya, A., Mpendo, J., Wambuzi, M., Nanvubya, A., Sigirenda, S., Kitandwe. P. K., Nielsen, L.E., Balyegisawa, A., Kaleebu, P., Nalusiba, J. and Sewankambo, N.K. (2014). High Incidence of HIV-1 Infection in a General Population of Fishing Communities around Lake Victoria, Uganda. *PLoS One* 9(5): 1-9.
- Lanoy, E., Mary-Krause, M., Tattevin, P., Perbost, I., Poizot-Martin, I., Dupont, C. and Costagliola, D. (2007). Frequency, determinants and consequences of delayed access to care for HIV infection in France. *Antivir Ther*, 12: 89-96.
- Levy, J. A. (1998). Caution: Should we be treating HIV infection early? *Lancet*, 352:982-983.
- Mocroft, A., Gatell, J., Reiss, P., Ledergerber, B., Kirk, O., Vella, S., Blaxhult, A., Phillips, A. N. and Lundgren, J. (2004). EuroSIDA study group. Causes of death in HIV infection: the key determinant to define the clinical response to anti-HIV therapy. *AIDS*, 18:2333-2337.
- Palella, F.J., Delaney, K. M., Moorman, A. C., Loveless, M.O., Fuhrer, J., Satten, G.A., Aschman, D.J., Holmberg, S. D. (1998). Declining morbidity and mortality among patients with advanced HIVinfection. *N. Engl J Med*, 338:853-860.
- Pérez-Alvarez, L., Villahermosa, M. L., Cuevas, M. T., Delgado, E., Manjón, N., Vázquez de Parga, E., Medrano, L., Contreras, G., Thomson, M. M., Colomo, C., Taboada, J. A. and Nájera, R. (2000). Single and multidrug resistance mutations to reverse transcriptase and protease inhibitors: HIV-1 infected patients from two geographical areas in Spain. Spanish Groups for Antiretroviral Resistance Studies. *J Hum Virol*, 3:150 - 156.
- Puig, T., Pérez-Olmeda, M., Rubio, A., Ruiz, L., Briones, C., Franco, M. J., Gómez-Cano, M., Stuyver, L., Zamora, L., Alvarez, C., Leal, M., Clotet, B., Soriano, V. (2000). Prevalence of genotypic resistance to nucleoside analogues and protease inhibitors in Spain. *AIDS*, 14:727-732.
- Quinn, C.T., Wawer, J.M., Sewankambo, N., Serwadda, D., Li, C., Wabwire-Mangen, F., Meehan, O. M., Lutalo, T. and Gray, H.R., (2000). Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1, *N. Engl. J. Med*, 342:921-92.

- Rawal, B. D., Degula, A., Lebedeva, L., Janssen, S.R., Hecht, F.M., Sheppard, W.H. and Busch, P. M. (2003). Development of a new less-sensitive enzyme immunoassay for detection of early HIV-1 infection. *J Acquir Immune Defic Syndr*, 33: 349-355.
- Sagay, A., Onakewhor, J., Galadanci, H. and Emuveyan, E. (2006). HIV status of partners of HIV positive pregnant women in different regions of Nigeria: matters arising. *Afr J Med Med Sci*, 35:125.
- Suligo, B., Massi, M., Galli, C., Sciandra, M., Di Sora, F., Pezzotti, P., Recchia, O., Montella, F., Sinicco, A. and Rezza, G. (2003). Identifying recent HIV infections using the avidity index and an automated enzyme immunoassay. *J Acquir. Immune Defic Syndr* 32(4): 424-428.
- Teck, R., Acurra, O., Gomani, P., Manzi, M., Pasulani, O., Kusamale, J., Salaniponi, F. M. L., Humblet, P., Nunn, P., Scano, F., Harries, A.D. and Zachariah, R. (2005). WHO clinical staging of HIV infection and disease, tuberculosis and eligibility for antiretroviral treatment: relationship to CD4 lymphocyte counts. *The International Journal of Tuberculosis and Lung Disease*, 9:258-262.
- UNAIDS/WHO, (2004). Joint United Nations Programme on HIV/AIDS and World Health Organization. UNAIDS/WHO policy statement on HIV testing. Geneva: UNAIDS <https://UNAIDS/WHO+policy+statement+on+HIV+testing.+Geneva:+UNAIDS&source=bl&ots=statement%20on%20HIV%20testing.%20Geneva%3A%20UNAIDS&f=false>.
- Valdiserri, R. O., Holtgrave, D. R. and West, G. R. (1999). Promoting early HIV diagnosis and entry into care. *AIDS*, 13:2317-2330.
- Weinhardt, L. S., Carey, M. P., Johnson, B. T. and Bickham, N. L. (1999). Effects of HIV counseling and testing on sexual risk behavior: a metaanalytic review of published research, 1985-1997. *Am. J. Public Health*, 89:1397-1405.
- World Health Organization. (2007). Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV related disease in adults and children. <http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf>. Accessed May 15, 2013.
- World Health Organization. (2005). Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance, 17-25.
- World Health Organization. (2013). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach: June 2013. Available at <http://www.who.int/hiv> (accessed 15 December 2014).
- Yazdanpanah, Y., Lange, J., Gerstoft, J. and Cairns, G. (2010). Earlier testing for HIV—1 how do we prevent late presentation? *Antivir Ther*, 15 Suppl 1: 17-24.
- Zachariah, R., Spielmann, M. P., Harries, A. D., Nkhoma, W., Chantulo, A. and Arendt, V. (2003). Sexually transmitted infections and sexual behaviour among commercial sex workers in a rural district in Malawi. *International Journal of STD and AIDS*, 14, 185-188.