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Casual Inference on the Assessment of the Direct and Indirect Effects of Latent Covariates on CD4 Cell Count Change among HIV Positive Adults under Treatment in the Amhara Region

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Abstract

Background: The use of structural equation modeling and latent variables remains unusual in epidemiology despite its potential usefulness and assessment of causal relations. Measuring the direct and indirect effect of latent variables helps with proper intervention and for the ART program to be effective. The main objective of the current investigation was to assess causal inference of assessment of the direct and indirect effect of latent covariates on CD4 cell count change for HIV positive adults under HAART.

Methods: Based on the repeated measures of CD4 cell count change data obtained in the ART section at Felege Hiwot teaching and specialized hospital, AMOS software was used for parameter estimation. The study was conducted on 792 randomly selected HIV positive adults. The data were collected by the health staff after a brief orientation of the variables under study.

Results: CD4 cell count change was directly and indirectly affected by the latent variables. The powers of effects of observed variables with and without latent variables were a little bit different from each other. Hence, the powerful effect of observed variables with latent variables was lower as compared to those without latent variables. The direct effect of latent variables on the response variable was a little bit greater than the indirect effect.

Conclusion: The power of the effects of observed variables was stronger than their effects with latent variables. Hence, the latent variables had significant contributions to the progress of CD4 cell count change. Health related education about the direct and indirect effects of latent variables should be given to patients under HAART. Knowledge of direct and indirect effects on the variable of interest is important for proper intervention in ART programs.

Keywords: Socio-demographic • Individual characteristics • Economic factors • Clinical variables • Structural equation modeling • CD4 cell count change

Abbreviations: RMSEA: Root Mean Square Error Analysis; HAART: Highly Active antiretroviral therapy; LGM: Latent Growth Model; CLGM: Covariate Latent Growth Model; HIV: Human Immunodeficiency Virus; SEM: Structural Equation Modeling; CFI: Comparative Fit Indices

Introduction

The causal effect of a treatment on health progression is generally mediated by several intermediate variables. Estimation of the parameters related to the causal effect of a treatment, that is mediated by a given intermediate variable is termed the indirect effect of the treatment [1]. On the other hand, the estimation of parameters when it is not mediated by the intermediate variable is termed the direct effect of the treatment [1]. Such a relation is often relevant to the understanding and to design of clinical and public health interventions. Estimation of the direct and indirect effect of a treatment on health progress is a crucial focus of epidemiological and clinical research and is major methodological advancement [2]. One of the well-known measures/ indicators of the health progression rate under HAART adherence are

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CD4 cell count change. To assess the various causal relations and effects, different authors proposed different approaches. One of the approaches is the presentation of a general locally efficient estimating function based on the methodology for estimation of the corresponding causal parameters. Another approach is to identify the pathways by which a treatment is acting and to quantify the component of the treatment's effect with and without a given intermediate variable (the indirect and direct effects of the treatment) [3]. Estimation of the direct and indirect effects of treatment helps in the understanding of the treatment's action and to design clinical and public health interventions. To compute the direct causal effect of treatment response, it is possible to assume the existence of counterfactual outcomes for a randomly selected individual [4]. The population direct effect is defined as the mean of these individual counterfactual direct effects [5,6]. On the other hand, in path analysis (structural equation modeling), one can see the direct, indirect, and total effects of the latent variables and the model do not assume that change is constant and linear. In path analysis, a unique additional contribution of a latent variable has been determined [7,8]. Identifying factors affecting the level of CD4 cell count change other than ART would help health professionals and patients to facilitate proper management and monitoring of the health care intervention on individuals with the highest risk (lowest CD4 cell count). Previously, research was conducted on predictors of CD4 cell count change using the classical statistics (PROC GLM ANOVA) model. However, in previous research, the effect of latent variables on the variable of interest is not investigated [9]. Previously, the effect of observed variables namely age, weight, baseline CD4 cell count, WHO stages, adherence, and follow-up visits on CD4 cell count change data are conducted using the same data by the same author using repeated measures, ANOVA. In such study, the effects of latent variables are not taken into account. The SEM analysis with PROC CALIS on the other hand allowed for explicit representation of measurement error and provided more information than the repeated measures ANOVA with PROC GLM [10]. The purpose of this study was, therefore, to investigate the causal inference of assessment of the direct and indirect effect of latent variables on longitudinal repeated measures of CD4 cell count change for HIV positive adults under HAART.

Materials and Methods

Study area

The study was conducted in Amhara Region, North-West Ethiopia, a case study at Felege-Hiwot Specialized and Referal Hospital.

Data source and study population: The data consists of retrospective longitudinal CD4 cell count data change/ progression obtained from 792 randomly selected HIV Positive adults who registered for the first 10 months of 2012 and followed up to 2017(five years of data). The study population belongs to HIV-positive adults whose follow-ups were from 2012 to 2017, the end of the study period.

Study design

The data used under the current investigation consists of secondary data and a retrospective longitudinal study design was employed.

Data collection procedures

The data were collected by the health staff for the primary interest of treatment follow-ups. The secondary data obtained at the ART section of the hospital was also collected by the health staff in consultation with the principal investigator.

Quality of data

This was conducted by data controllers in the ART section of the hospital. The controllers were taken intensive training by the Ministry of Health for different purposes. The reliability of variables was assessed using Cronbach's alpha and the variables included in the study were tested for consistency of understanding and the completeness of the data items on 75 random samples. Necessary amendments were made to the final data collection sheet.

Variables under study

Response variable: The longitudinal response variable for the current study was the CD4 cell count change recorded at each visiting time. CD4 cell count change was defined as the change/ or progressions obtained at each visiting time which was obtained by considering the CD4 cell count at the current visit and the CD4 cell count recorded immediately before the current visit.

Predictor variables: From the medical records of each HIV positive patient, social characteristics, individual behaviors, clinical factors, HAART adherence competence, and retention in HAART medication were recorded. The association for predictor variables, taken from charts of patients is indicated in Figure 2.

The Structural Equation Model (SEM) was used to assess the direct and indirect effect of latent variables on the variable of interest. Complex relationships have existed between CD4 cell count change and observed and latent variables. The casual relations and direct and indirect effects of latent variables on the variable of interest were assessed. Unlike conventional regression methods, SEM enables us to deal with such complex relationships and estimate the direct and indirect effects of the variables of interest.

In the current investigation; the variables such as religious affiliation, ethnicity, and migration that cannot be measured directly from patients' data were considered as socio-demographic latent variables. Economic factors such as access to drinking water, electric city, and employment status not included in the data are also considered latent variables. Clinical factors like viral load progression, depression of patients because of medication, medication allergies, and patient-health staff relations were considered as clinical latent variables. Similarly, individual factors such as physical exercise, refreshment of him/her, life experience, cognitive style, and biological and genetic factors were considered individual variables that cannot be measured directly and are treated as latent variables. Latent variables (socio-economic variables) were hypothesized to depend on education level, residence area, marital status, and disclosure level of disease. The latent variable (economic factor) was hypothesized to depend

on income level and ownership of cell phones, Individual characteristics were hypothesized to depend on weight, age, and sex, and clinical factors were hypothesized to depend on WHO stages adherence level, and baseline CD4 cell count.

Similarly, the latent variable retention in HAART medication care was hypothesized to be dependent on follow-up visits, socio-demographic factors, economic factors, and individual characteristics. The latent covariate, HAART adherence competence was hypothesized to be dependent on clinical factors and retention of HAART medication care. Finally, CD4 cell count change was hypothesized to be dependent on retention in HAART medication care and HRRAT adherence competence directly and to be dependent indirectly on the other covariates. In this study, the observed variables like age, weight, visiting times, and baseline CD4 cell count were constructed on latent variables (Socio-demographic, economic, individual, and clinical variables).

Socio-demographic and clinical factors were also constructed for another latent variable, HAART medication care and real biological, psychological, and HAART adherence competence. The retention in medication adherence and adherence competence were constructed to the variable of interest. The effect of exogenous variables on the variable of interest was measured based on the estimates of parameters that existed between the exogenous and endogenous variables. The effect of exogenous variables on the variable of interest is also measured based on the amount of variance of errors created during estimation. This was constructed using AMOS software version 22. The software computed the values of parameters, the variance of error terms, and disturbance terms (D1, D2, D6). Data analysis was carried out to obtain descriptive statistics (means and Standard Deviations (SD)) for each of the independent variables. Finally, using structural equation modeling, several trajectory analyses were conducted with which the direct and indirect relationship among variables can be specified.

Application of guidelines and regulations: The study was performed in accordance with relevant guidelines and regulations.

Results

Among all the sample of 792 patients: 40.9% were rural residents; 50.6% were females; 56.3% were living with their partner; 33.6% disclosed their disease to family members, 49.2% were owners of cell phones, 25.5% were medication adherent, only 11.5% had high income and 20.6% had no education. The average (median) weight of all patients was 58 kg (IQR: (52, 64)), average years of all patients was 36 years (IQR: (28, 48)).

The estimate of regression coefficients was conducted using the maximum likelihood estimation technique and indicated in hypothesized path analysis as shown in Figure 1.

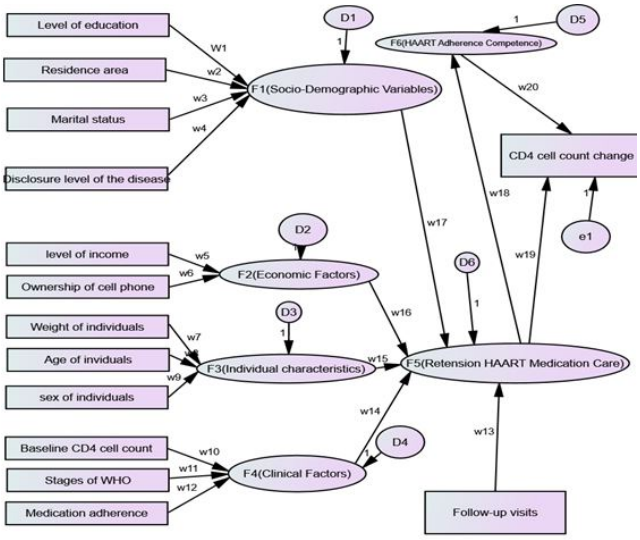

Figure 1. Path analysis for assessment for direct and indirect effect of covariates on CD4 cells count change.

Figure 1 revealed that C.R=Estimates/S.E was greater than 1.96 for a 0.05 level of confidence and greater than 2.56 for a 0.01 level of confidence for all covariates and this further indicates that latent variables had direct and indirect effects on the CD4 cell count change [11,12].

In the hypothetical relationships described in Figure 2, non-recorded variables at each visiting time were categorized as socio-demographic, economic, individual characteristics, and clinical factors. The magnitude of parameter estimation was conducted using AMOS version 22 as indicated in Figure 2.

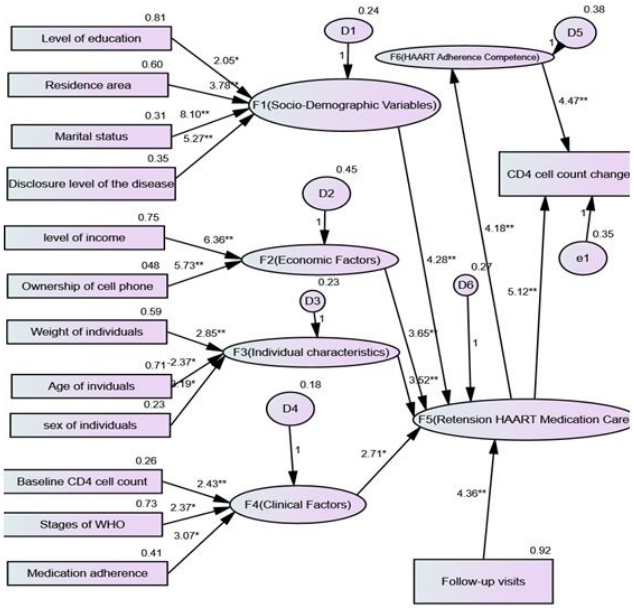

Figure 2. Parameter estimation direct and indirect effect of covariates on CD4 count change.

Figure 2 indicates that socio-demographic factors had a direct and significant effect on retention medication care (F5) with a regression coefficient of 4.28 and p-value=0.0021). Similarly, economic and individual factors had a direct and significant effect on the retention of medication care (F5) with a regression coefficient of 3.65 and 3.52 for each with p-values=0.0012 and p-value=0.023

respectively. The latent variable retention HAART medication care had a significant and direct effect on another latent variable HAART adherence competence (F6) with a regression coefficient of 4.18, p-values=0.0021. Similarly, clinical factors also had a direct and significant effect on HAART adherence competence (F6). Finally, the latent variables, retention of HAART medication care, and HAART adherence competence had direct and significant effects on the variable of interest (CD4 cell count change). The hypothetical relations in Figure 1, also indicate that the latent variables namely, socio-demographic factors (F1), economic factors (F2), individual factors (F3), and clinical factors (F4) had an indirect effect on the CD4 cell count change. Figure 2 also indicates that the observed variables like level of education, residence area, marital status, and disclosure of the disease to community living together had a direct and significant effect on the latent variable, socio-demographic factors (F1). The observed variables, level of income and ownership of cell phone significantly affected economic factors (F2). Age and sex of patients affected significantly another latent variable (individual factors (F3)). Baseline CD4 cell count, WHO stages and adherence level significantly affected clinical factors. The observed covariate, follow-up visits had a significant effect on the latent covariates' retention of HAART medication care (F5). Hence, latent variables that can't be measured directly also had direct and indirect effects on CD4 cell count change. In the estimation of the covariance structure, key indicators of goodness-of-fit provided that *chi-square*=983.45, with a p-value for *chi-square* <0.01, which indicates that the *chi-square* statistic is not closer to zero and the corresponding p-value is very small (significant), which is an indicator of weak fit. This indicates that the model is inadequate. However, RMSEA was estimated to be 0.01, CFI=0.97, Non-Normed Fit Index (NNFI)=0.96, and NFI=0.95. Hence, RMSEA, CFI, and NFI assured for the model to be a good fit. The *chi-square* probability for current repeated data indicates an unacceptable model fit (*chi-square*=9.101, df=3, p=0.028). The difference between observed and expected covariance structure matrices under the current investigation was measured using the *chi-square* value. The model under the study was also determined using *chi-square* the value was close to zero and the corresponding probability value was greater than 0.05. Hence, the value for RMSEA was 0.123 which indicates that the model was unacceptable. On the other hand, the value for CFI was 0.998 and the corresponding value of NNFI was 0.988 which indicates that the model was acceptable to fit the data in the current investigation with a value greater than 0.90 (Table 1) [13,14].

Variable	Estimates	Standard deviation	Z-values
Level of education	2.05	0.9	25.32
Residence area	3.78	0.77	21.76
Marital status	8.1	0.567	22.04
Disclosure level of the disease	5.27	0.592	15.25
Level of income	6.36	0.87	10.4
Ownership of cell phone	5.73	0.693	20.98
Weight of individuals	2.85	0.768	27.47
Age of individuals	-2.37	0.843	-27.43
Sex of individuals	2.19	0.48	19.71
Baseline CD4 cell count	2.43	0.51	23.57
Stage of WHO	2.37	0.854	24.39
Medication adherence	3.07	0.64	16.17
Follow-up visits	4.36	0.959	21.45
Socio-demographic variables	4.28	0.49	18.25
Economic variables	3.65	0.671	20.17
Individual factors	3.52	0.48	17,62
Clinical Factors	2.71	0.424	14.52
Retention HAART medication care	4.18	0.52	18.25
HAART adherence competence	4.47	0.616	23.41

Table 1. Structural Equation Modeling (SEM) for estimation of parameters.

Direct and Indirect effect of latent variables

The latent covariates, socio-demographic, economic, individual, and clinical factors, retention in HAART medication care, and HAART adherence competence had a direct and indirect effect on the CD4 cell count change. The direct and indirect effects are indicated in Table 2.

Effect	Direct effect		Indirect effect	
	Estimate	S.E	Estimate	S.E
Socio-demographic Variables	0.854	0.341	0.421	0.032
Economic factors	0.643	0.453	0.405	0.453
Individual characteristics	0.728	0.432	0.352	0.422
Clinical Factors	0.526	0.273	0.435	0.272
HAART adherence competence	0.836	0.543	0.654	0.543
Retention in HAART medication care	0.725	0.546	0.643	0.546

Table 2. Direct and indirect effect of latent covariates on CD4 cell change.

Table 2 indicates that the effect of latent variables which belongs to the direct effect was a little bit greater than indirect effects. Hence, CD4 cell count change had been affected by the direct and indirect involvement of latent variables.

Comparison of predictors of CD4 cell count change with and without latent variables

The comparison of approaches was conducted considering latent variables and without latent variables. Figure 2 indicates that some of the variables are manifest and others are latent. To compare approaches, the effect of observed variables without latent was compared with latent variables. The effect of manifest variables like level of education, marital status, sex of patients, disclosure of the disease to community living together, ownership of cell phone, level of income, weight, age, sex of patients, baseline CD4 cell count, WHO stages, adherence level and visiting times were potential predictors of CD4 cell count change without any latent variables using the same data and same study area. In the current investigation, it was possible to compare the effect of these manifest variables with and without latent variables, conducted previously by the same author, data, and same study area [15]. A baseline measurement and its change had different residual errors. The measurement model for each sex was verified and the result in the loadings and the fit indices were approximately similar while parameterization with and without equality of constraints

A combination of repeated measurements was considered by the latent variable analysis and the result makes the latent variables vary together. Hence, the individual measurement analysis gave the same conclusion which was not achieved in the analysis conducted without a latent variable approach. This implies that whenever the individual analyses are not consistent, a latent variable model provides an easily interpretable synthesis.

Discussion

In the current investigation, the association of socio-demographic, individual characteristics, and clinical variables were investigated using SEM (path analysis).

The result of this investigation revealed that socio-demographic factors, economic factors, and individual characteristics have direct and significant associations with retention in the HAART program. This finding agreed with one of the previous investigations [16]. Therefore, socio-demographic disadvantageous HIV positive adults are related to lower CD4 cell count change.

Education is to a large extent correlated with socio-demographics and much of the complexity that is evident in the relationship between income and HIV prevalence is also evident in the relationship between education and HIV prevalence. Hence, relatively uneducated patients are less likely to know what AIDS is and how HIV is transmitted from one to another [17].

The relationship between marital status and HIV infection is complex. Hence, the risk of HIV prevalence remained significantly high among unmarried compared with married people when only sex behavior factors are controlled for the given model [18].

The adherence level of patients is highly associated with socio-demographic characteristics such that patients who disclosed their disease to the community living with them had good competence levels of food and medication adherence [19]. Thus, it is said that a person who disclosed the disease to people living together may get social support from the community and might have good medication adherence and this further leads to improvement of the CD4 cell count change in successive visits [20]. The social support given to HIV patients who disclosed their disease helps to have very good retention in HIV medication care which is a crucial activity for achieving long-term survival with the virus.

Similarly, clinical factors such as baseline CD4 cell count, WHO stages, and adherence level had a direct and significant effect on HAART adherence competence. Hence, HIV positive adults with good adherence levels, high baseline CD4 cell count, and WHO stage I had good HAART adherence competence as compared to WHO stage IV. This result is similar to previously conducted research.

Retention in medication care have also direct and significant effect on HAART adherence competence which means patients who closely follow their prescribed medication given by the health staff had good adherence competence. This result agreed with previous research.

The economic factors such as patients with cell phones and those who had high incomes associated with high retention in medication care. Hence, patients with high income may use different alternatives to get pills and he/she also uses proper food adherence schedules for the treatment to be effective and this encourages the patient to attend visits to health institutions. Cell phones of patients can play a significant role in taking pills on time and reminding the date that the patient should visit the hospital and this has an indirect effect on the status of CD4 cell count change. Cell phones helped patients to be HAART adherent because of their alarm (memory aid) for reminding the time pills are taken. This finding is consistent with findings from another study and suggests the need for making cell phones available to needy HAART attendants. This finding is also consistent with previously conducted research.

Clinical factors such as patients' baseline CD4 cell count significantly affected their retention of medication care. Patients with a high baseline CD4 cell count are encouraged the patient to be HAART adherent as compared to patients with less baseline CD4 cell count. This result indicates that clinical factors (CD4 cell count and WHO stages) are positively associated with the retention of medication care.

Finally, retention in medication care and adherence competence had a direct and significant effect on the variable of interest (CD4 cell count change) which has a similar argument to previous research.

Poor adherent patients had low results in the variable of interest which indicates that adherence to HAART and CD4 cell count change are positively correlated with each other. Patients with good performance of adherence to medication had better CD4 cell count change. The current study indicates that the variable of interest (CD4 cell count change) increased over time. However, its progress was different for different groups. When a single measurement exhibits a relationship with the latent variable, considering several measurements have much gain and a latent variable are recommended rather than separate analyses of each indicator. Structural equations and path analyses are very useful for causal interpretation. Of course, the interpretations are conditional on the validity of the assumed model. A single intervention strategy cannot improve the risks of HIV patients.

Conclusion

In conclusion, latent variable and structural equation models enabled us to present synthetic results rather than separate analyses and to perform a detailed analysis of the causal mechanisms involved.

The result of the current investigation corroborates key factors like a realistic assessment of patients' knowledge/level of education and understanding causal inference of the direct and indirect effects of latent variables on the study variable, CD4 cell count change. Hence, the current research endeavored to identify certain groups that require special attention; and this helps to intervene in the HAART program to be effective and elongate patients` lives with the virus. Moreover, interventions need to be designed to promote early HIV testing and early enrollment of HIV infected individuals into ART services. Health related issues about socio-demographic, economic, individual characteristics, and clinical factors, improving public awareness through advocacy and social mobilization should be included in the ART services. It is strongly recommended that underline the need for ART in HIV infected patients for immune reconstitution.

Ethical Clearance and Consent for Participants

Since the data was secondary and there was no chance of getting participants, consent for participants was not obtained from respondents. However, to get the secondary data from the hospital in the study area, an Ethical clearance certificate had been obtained from two universities namely Bahir Dar University, Ethiopia with Ref RCS/1412/20012. I can attach the ethical clearance certificate up on request.

Competing Interests

There is no conflict of financial and non-financial interest between authors or between authors and institutions.

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Not applicable

Authors' Contributions

The first and corresponding author wrote the proposal, developed the data collection format, supervised the data collection process, and analyzed and interpreted the data.

Availability of Data and Materials

I confirm that the data used for this study is available at the corresponding authors and can be submitted upon request.

Consent for Publication

This manuscript has not been published elsewhere and is not under consideration by any other journal. An author approved the final manuscript and agreed with its submission to this journal.

References

1. Beyene, Melkamu Bedimo, and Habtamu Bedimo Beyene. "Predictors of late HIV diagnosis among adult people living with HIV/AIDS who undertake an initial CD4 T cell evaluation, northern Ethiopia: a case-control study." *PloS one* 10 (2015): 0140004.
2. Tegegne, Awoke Seyoum, Principal Ndlovu, and Temesgen Zewotir. "Determinants of CD4 cell count change and time-to default from HAART; a comparison of separate and joint models." *BMC Infect Dis* 18 (2018): 1-11.
3. Adams, Mustapha, and Albert Luguterah. "Longitudinal analysis of change in CD4+ cell counts of HIV-1 patients on Antiretroviral Therapy (ART) in the Builsa district hospital." *Eur Sci J* 9 (2013): 1.
4. Muthen, Bengt, and Tihomir Asparouhov. "Causal effects in mediation modeling: An introduction with applications to latent variables." *Struct Equ Modeling Multidisci J* 22 (2015): 12-23.

5. Katunaric, Vjeran. "Od egalitarnog sindroma do izvrsnosti: O nacinima legitimiranja društvenih nejednakosti." *Politicka misao* 48 (2011): 11-34.
6. Louizos, Christos, Uri Shalit, Joris M Mooij, and David Sontag, et al. "Causal effect inference with deep latent-variable models." *Adv Neural Inf Process Syst* 30 (2017).
7. Cheung, Gordon W , and Rebecca S Lau. "Testing mediation and suppression effects of latent variables: Bootstrapping with structural equation models." *Organ Res Methods* 11 (2008): 296-325.
8. Lleras, Christy. "Path analysis." *Encyclopedia Soc Measure* 3 (2005): 25-30.
9. Asfaw, Addisu, Dagim Ali, Tadele Eticha, and Adissu Alemayehu, et al. "CD4 cell count trends after commencement of antiretroviral therapy among HIV infected patients in Tigray, Northern Ethiopia: a retrospective cross-sectional study." *PloS One* 10 (2015): 0122583.
10. Guerrero, Josep M, Juan C Vasquez, Jose Matas, and Luis Garcia De Vicuna, et al. "Hierarchical control of droop-controlled AC and DC microgrids-A general approach toward standardization." *IEEE Trans Ind Electron* 58 (2010): 158-172.
11. Marsh, Herbert W, and Dennis Hocevar. "Application of confirmatory factor analysis to the study of self-concept: First and higher order factor models and their invariance across groups." *Psychol Bull* 97 (1985): 562.
12. MacCallum, Robert C, and James T Austin. "Applications of structural equation modeling in psychological research." *Annu Rev Psychol* 51 (2000): 201-226.
13. Roth, David L, Deborah J Wiebe, Roger B Fillingim, and Kathleen A Shay, et al. "Life events, fitness, hardiness, and health: A simultaneous analysis of proposed stress-resistance effects." *J Pers Soc Psychol* 57 (1989): 136.
14. Duncan, Terry E, Susan C Duncan, Anthony Alpert, and Hyman Hops, et al. "Latent variable modeling of longitudinal and multilevel substance use data." *Multivariate Behav Res* 32 (1997): 275-318.
15. Hu, Li-tze, and Peter M Bentler. "Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives." *Struct Equ Modeling Multidisci J* 6 (1999): 1-55.
16. Bayou, Tigist, Minyahil Woldu, Gebrehiwot G Meskel, and Haftay Mezgebe, et al. "Factors determinant for change of initial antiretroviral treatment regimen among patients on ART follow-up clinic of Mekelle Hospital, Mekelle, Ethiopia." *Int J Basic Clin Pharmacol* 3 (2014): 44-49.
17. Do, Natalie T, Kelesitse Phiri, Hermann Bussmann, and Tendani Gaolathe, et al. "Psychosocial factors affecting medication adherence among HIV-1 infected adults receiving combination Antiretroviral therapy (cART) in Botswana." *AIDS Res Hum Retroviruses* 26 (2010): 685-691.
18. Langebeek, Nienke, Elizabeth H Gisolf, Peter Reiss, and Sigrid C Vervoort, et al. "Predictors and correlates of adherence to combination antiretroviral Therapy (ART) for chronic HIV infection: A meta-analysis." *BMC Med* 12 (2014): 1-14.
19. Nosyk, Bohdan, Lillian Lourenço, Jeong Eun Min, and Dimitry Shopin, et al. "Characterizing retention in HAART as a recurrent event process: insights into 'cascade churn'." *AIDS* 29 (2015): 1681.
20. Schwimmer, Jeffrey B, Tasha M Burwinkle, and James W Varni. "Health-related quality of life of severely obese children and adolescents." *JAMA* 289 (2003): 1813-1819.

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