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Advanced HIV Disease among Males and Females Initiating HIV Care in Rural Ethiopia

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Abstract

Despite recommendations for rapidly initiating HIV treatment, many persons in sub-Saharan Africa present to care with advanced HIV disease. Baseline survey and clinical data were collected on 1799 adults newly enrolling at 32 district hospitals and local health HIV clinics in rural Ethiopia. Among those with complete HIV disease information, advanced HIV disease (defined as CD4 count <200 cells/mm^3 or World Health Organization [WHO] HIV clinical stage III or IV disease) was present in 66% of males and 56% of females ($P < .001$). Males (compared to females) had lower CD4 counts (287 cells/mm^3 versus 345 cells/mm^3), lower body mass index (19.3 kg/m^2 versus 20.2 kg/m^2), and more WHO stage III or IV disease (46% versus 37%), ($P < .001$). Men reported more chronic diarrhea, fevers, cough, pain, fatigue, and weight loss ($P < .05$). Most initiating care in this resource-limited setting had advanced HIV disease. Men had poorer health status, supporting the importance of earlier diagnosis, linkage to care, and initiation of antiretroviral therapy.

Keywords

HIV, advanced HIV disease, sub-Saharan Africa, CD4 count, gender

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What Do We Already Know about This Topic?

Despite current recommendations that all persons living with HIV should initiate treatment at the earliest possible stage, a significant proportion of persons, especially in developing countries, have advanced HIV disease when they first enter care.

How Does Your Research Contribute to the Field?

Among HIV-positive patients new to care at primarily rural district hospitals and local health centers in Ethiopia, most (60%) already had advanced HIV disease upon presenting to care, with males significantly more likely to present with advanced clinical and/or immunologic disease.

What Are Your Research's Implications toward Theory, Practice, or Policy?

There is a strong need for implementation and evaluation of innovative strategies to ensure that all HIV-positive persons, including men, receive earlier diagnosis, linkage to care, and initiation of antiretroviral therapy, to help them remain healthy and disease-free.

Of the estimated 36.9 million people living with HIV (PLWH), 21.7 million were on antiretroviral therapy (ART) as of 2017.[1] Those who initiate ART at low CD4 counts have a reduced survival probability, as well as an increased risk of developing serious HIV-related clinical outcomes.[2-4] Advanced HIV disease and delayed ART may be associated with increased levels of immune activation and inflammation, risk factors for serious non-AIDS events such as cardiovascular disease.[5-7] Earlier ART has been associated with enhanced CD4 cell recovery and normalization of immune status.[2,8,9] HIV treatment with viral load suppression also greatly reduces the probability of onward sexual transmission[10] and in pregnant women significantly prevents perinatal transmission.[11] Therefore, PLWH who initiate

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ART earlier in HIV infection with higher CD4 counts have reduced morbidity and mortality, plus a decreased risk of transmitting HIV to others. For these reasons, current guidelines state that all HIV-infected persons be on ART, initiating treatment as soon as possible.[12,13]

Despite these recommendations, a significant proportion of PLWH, especially in developing countries, have advanced disease when first diagnosed.[14-26] According to one global analysis, the modeled median CD4 count at ART initiation in 2015 was 327 cells/mm^3 in high-income countries, 234/mm^3 in lower middle-income countries, and 287/mm^3 in low-income countries.[14] Recommending early treatment for all PLWH will have reduced benefits if large numbers continue to first present with low CD4 counts and late-stage HIV disease. The World Health Organization (WHO) has also outlined an expanded package of interventions, specifically for those persons presenting with advanced HIV disease.[13] To most effectively target strategies to reduce global HIV morbidity and mortality, it is therefore important to identify those populations at highest risk for late presentation to HIV care.

During 2015 to 2017, we began a cluster randomized trial in Ethiopia and enrolled 1799 PLWH who were new to HIV care at one of 32 primarily rural district hospitals and local health centers.[27] The purpose of this study was to assess an intervention utilizing community support workers to help promote retention in care over a 3-year follow-up. In this analysis, we describe baseline clinical characteristics of participants in this study, specifically focusing on the proportion presenting late to care with advanced HIV disease. Because a number of studies have indicated that men present to care with more advanced HIV disease than women,[14,16-18,21,23-26] we were particularly interested in evaluating gender differences in clinical symptoms and CD4 count upon enrollment in care.

Methods

Study Participants

This study was conducted in the Southern Nations, Nationalities, and Peoples' Region (SNNPR) of Ethiopia, one of this country's most rural of the major regions. In Ethiopia, primary care is provided through a network of geographically dispersed health centers typically staffed by clinical officers and nurses; secondary care is provided at district hospitals typically staffed by physicians. HIV care in Ethiopia, initially rolled out in hospital HIV clinics, is also being decentralized to local health centers as part of the national HIV plan.[28] From a list of health facilities in SNNPR, we selected 16 district hospitals and 16 health centers that in previous years had provided care to the largest numbers of PLWH; all facilities were in the public sector and under direction of the SNNPR Regional Health Bureau. Procedures for cluster randomization of our intervention and control sites have been previously described.[27]

Because studies from Ethiopia and other African countries indicate that nonretention in care is greatest in the first 6 months after ART initiation,[29] our inclusion criteria for this study evaluating HIV retention in care were adults ($\geq$18 years of age) who had newly enrolled at one of our participating sites within the previous 3 months. The initial invitation to participate for those who met inclusion criteria was done by the clinic nurse at the end of a patient's visit, with a follow-up appointment and informed consent then obtained by the study coordinator. From October 2015 through April 2017, the initial invitation to participate was given to 1952 PLWH who met inclusion criteria, of whom 1815 scheduled follow-up appointments with a study coordinator to learn more about this study, and 1799 (92%) ultimately agreed to enroll.[27] Most who did not schedule a follow-up appointment could not be reached because they lacked cell phones or other contact information to schedule a meeting and/or lived a far distance from the clinic.

Measurements

A baseline survey was verbally administered to all participants in Amharic and included questions on demographics (eg, age, gender, marital status, occupation) and presence of 6 physical symptoms (fever, pain, cough, fatigue, diarrhea, weight loss) lasting for more than 1 month (defined as chronic). Participants were also asked about their ability to carry out normal activities and take care of their personal needs, using classifications adapted from the top 6 categories (50-100) of the Karnofsky Performance Status scale.[30] In addition, participants gave permission to have the following baseline information abstracted from their HIV clinic record: height and weight (to calculate body mass index [BMI]), CD4 count, and WHO HIV clinical stage.[31]

Analysis

Associations between clinical status and gender were assessed using simple descriptive statistics, χ^2, and t test. As defined by WHO, advanced HIV disease was classified as the presence of either a CD4 count <200 cells/mm^3 or the presence of WHO HIV clinical stage III or IV disease.[13] Crude associations between demographic characteristics and advanced HIV disease were also estimated using descriptive statistics and relative risks (RRs) with 95% confidence intervals (CIs). Multivariate analysis was performed using Poisson regression with a robust variance estimator to evaluate the association between gender and advanced HIV disease, adjusting for all other demographic characteristics. Poisson regression to estimate RR was chosen instead of logistic regression (which produces odds ratios) because odds ratios are known to overestimate RR when the prevalence of the outcome is common, as in this analysis.[32]

Ethics

All participants provided informed consent. All data collection forms included only the participant identification number; no personal identifiers were recorded. Approval was obtained

from the University of Minnesota's institutional review board and the Ethiopian Ministry of Science and Technology National Research Ethics Committee.

Results

Study Participants

From October 2015 to April 2017, 1799 PLWH enrolled in this study. Of these, 1066 (59%) were female and 733 (41%) male; the mean age was 34.1 years. Forty-nine percent were married, 15% single and 35% divorced, widowed or separated. The most common occupations were day laborer (17%), farmer (16%), housewife (14%), business person (eg, merchant; 14%), private employee (14%), and civil servant (8%); 11% were unemployed. In terms of education, 26% never went to school, and 37% completed some (but not all) 8 years of primary education. The most common religions were Christian Orthodox (48%), Protestant (38%), and Muslim (11%).

When asked about the presence of physical symptoms lasting for more than 1 month, 67% reported weight loss, 66% chronic fatigue, 43% chronic fevers, 38% chronic pain, 37% chronic cough, and 20% chronic diarrhea; over half (55%) of participants reported 3 or more of these symptoms. Upon enrollment in care, the mean BMI was 19.8 kg/m^2, with 37% having a BMI <18.5 kg/m^2 (defined as underweight) and 25% having a BMI $\leq$17.5 kg/m^2. When asked about their functional status, 65% could carry out normal activities such as work or shopping (without or with minor symptoms), 19% could carry out normal activities but with effort, and 16% were unable to carry out their normal activities.

When first seen in clinic, 40% were classified as WHO HIV clinical stage I, 19% as stage II, 35% as stage III, and 6% as stage IV. For 1421 participants, a baseline CD4 count was collected and recorded; for some patients, including those from smaller health clinics, a CD4 count was not immediately available before starting therapy. For those who had this result, the mean CD4 count upon enrolling in care was 322 cells/mm^3; 39% had <200 cells/mm^3, 24% had 200 to 350 cells/mm^3, and 37% had >350 cells/mm^3.

Of all participants in this study, 942 were known to have either WHO HIV clinical stage III or IV disease or a CD4 count <200 cells/mm^3, meeting the WHO definition for advanced HIV disease; an additional 617 participants were documented as having both WHO HIV clinical stage I or II disease and a CD4 count $\geq$200 cells/mm^3. Therefore, for 1559 PLWH, we were able to define the presence (60%) or absence (40%) of advanced HIV disease upon entry into care. The remaining 240 (13%) were either WHO stage I/II or had $\geq$200 CD4 cells/mm^3 but lacked both pieces of baseline information documented in their medical records; the proportion missing such missing information was similar in both males (13%) and females (14%; $P > .10$).

Clinical Status by Gender

As shown in Table 1, differences between men and women were present for a variety of physical health parameters. Eight-seven percent of men and 82% of women reported at least 1 of the 6 chronic disease symptoms ($P = .008$); men were more likely to report each of these 6 chronic symptoms. Women reported being more likely to carry out normal activities without requiring extra effort. The mean BMI upon enrollment was lower for men than women (19.3 kg/m^2 for males versus 20.2 for females [$P < .001$], with males more likely to have a BMI <18.5 kg/m^2 [underweight; $P < .001$). Forty-six percent of males entering care were classified as having a WHO HIV clinical stage III or IV disease, compared to 37% of females (RR = 1.27, 95% CI, 1.13-1.42, $P < .001$). Among those persons who had a CD4 count at the time of enrollment in care, the mean CD4 was 287 cells/mm^3 for males versus 345 cells/mm^3 for females ($P < .001$). A CD4 count <200 cells/mm^3 was present in 43% of males and 37% of females (RR = 1.16; 95% CI, 1.02-1.32, $P = .025$; Table 1).

Table 1. Clinical Signs, Symptoms, and Indicators of Advanced HIV Disease[a] among 1066 Females and 733 Males Newly Enrolling in Care at 1 of 32 District Hospital or Local Health Center HIV Clinics in Rural Southern Ethiopia, 2015 to 2017.[b]

Clinical Signs/Symptoms	Males, n (%)	Females, n (%)	*P* Value
Chronic diarrhea >1 month	170 (23)	186 (17)	.003
Chronic fever >1 month	348 (47)	430 (40)	.003
Chronic cough >1 month	318 (43)	338 (32)	<.001
Chronic pain >1 month	300 (41)	385 (36)	.039
Chronic fatigue >1 month	512 (70)	683 (64)	.012
Weight loss >1 month	516 (70)	691 (65)	.013
Reported none of 6 chronic symptoms	97 (13)	191 (18)	.008
Can carry out normal activities without extra effort	448 (61)	727 (68)	.001
Body mass index <18.5 kg/m^2	304 (43)	346 (34)	<.001
WHO HIV clinical stage III or IV	337 (46)	386 (37)	<.001
CD4 count <200 cells mm^3	242 (43)	312 (37)	.025
Advanced HIV disease	424 (66)	518 (56)	<.001

Abbreviation: WHO, World Health Organization.
[a]Advanced HIV disease defined as World Health Organization HIV clinical stage III or IV disease, or CD4 count <200 cells mm^3.
[b]Missing data excluded from analysis.

Of 1559 participants who met our definition for the presence or absence of advanced HIV disease upon enrollment in care, 66% of males and 56% of females had advanced HIV disease (RR = 1.18, 95% CI, 1.09-1.27, $P < .001$; Table 1). Those presenting with advanced HIV disease were also significantly more likely to be age 26 years or older and unemployed (Table 2). In multivariate analysis adjusting for other demographic variables in Table 2, male gender remained significantly associated with advanced HIV disease (adjusted RR = 1.20, 95% CI, 1.10-1.31, $P < .001$), along with unemployment (adjusted RR = 1.28, 95% CI, 1.15-1.42, $P < .001$); those $\leq$25 years of age were less likely to have advanced HIV disease (adjusted RR = 0.83, 95% CI, 0.74-0.94, $P = .001$).

Discussion

Among almost 1800 Ethiopian HIV-positive patients new to care at one of 32 primarily rural district hospitals and local

Table 2. Proportion of Those with Advanced HIV Disease[a] Newly Enrolling in Care at 1 of 32 District Hospital or Local Health Center HIV Clinics in Rural Southern Ethiopia, 2015 to 2017, by Selected Demographic Characteristics.[b]

Demographic Characteristics	Without Advanced HIV Disease, n (%)	With Advanced HIV Disease, n (%)	*P* Value
Gender			<.001
Male	216 (34)	424 (66)	
Female	401 (44)	518 (56)	
Age group, years			.002
≤25	171 (48)	188 (52)	
26-44	361 (37)	614 (63)	
≥45	76 (38)	124 (62)	
Marital status			.31
Single	83 (36)	145 (64)	
Married	321 (41)	454 (59)	
Widowed/divorced/ separated	212 (38)	340 (62)	
Education			.74
No school	156 (40)	232 (60)	
Some primary school	297 (40)	442 (60)	
Above primary school	164 (38)	267 (62)	
Employment			<.001
Currently employed[c]	550 (41)	782 (59)	
Currently unemployed	48 (27)	131 (73)	

[a]Advanced HIV disease defined as World Health Organization HIV clinical stage III or IV disease, or CD4 count <200 cells mm^3.
[b]Missing data excluded from analysis.
[c]All occupations, including housewives and day laborers.

health centers throughout southern Ethiopia, our study concluded that among those with available information on advanced HIV disease status, 60% already had advanced HIV upon presenting to care. Although over half of both men and women had advanced disease, males were significantly more likely to present with WHO HIV stage III or IV disease and with CD4 counts of <200 cells/mm^3. Consistent with these findings, men were more likely to have a range of chronic physical symptoms and lower BMI when entering care. The association of advanced HIV disease with male gender remained after adjusting for other demographic characteristics, including age, education, and employment status.

Our finding that many Ethiopian HIV-positive patients present to care with more advanced HIV disease is consistent with other reports from many developing countries, including in sub-Saharan Africa (SSA).[14-26] One meta-analysis from multiple African countries reported a median CD4 count in 2002 of 251 cells/mm^3 at presentation to care and 152 cells/mm^3 at ART initiation, with no significant increase in CD4 counts through 2013.[15] Another study from 4 African countries found that in 2011, 18% of those enrolling in care and 29% of those initiating ART had a CD4 count <100 cells/mm^3 or WHO disease stage IV.[16] Of those initiating ART in 6 Ethiopian clinics during 2012 to 2013, 27% had either <150 CD4 cells/mm^3 or WHO stage IV disease at enrollment in HIV care.[21]

Reasons for late presentation to care may be multiple and include either decreased knowledge of HIV status due to lack of testing or poor linkage to care. Summary data from eastern and southern Africa for 2017 indicated that only 76% of all PLWH knew their HIV status and that only 60% had been linked to care and started on treatment, representing challenges in meeting the UNAIDS 90-90-90 goals.[33] Ethiopia has made considerable progress over the past decade in meeting UNAIDS goals, although gaps remain. Two comprehensive analyses of data estimated that in 2016, of all PLWH in Ethiopia, 67% to 79% knew their HIV status and 59% to 71% were on ART.[34,35] One recent analysis reported significant regional variation, with an estimated 58% of PLWH in SNNPR on ART in 2017, compared to the national average of 71%.[36] In a survey we conducted in one rural Ethiopian community in SNNPR, failure to test was associated with multiple factors, including lack of awareness about benefits of ART and the belief that HIV-infected persons would be stigmatized by their communities.[37]

Our results are consistent with other studies finding that men are more likely than women to present with advanced HIV disease.[14,16-18,21,23-26] An analysis of data from 6 Ethiopian urban clinics found that men were twice as likely as nonpregnant women to have a CD4 count <150 cells/mm^3 or WHO stage IV disease.[21] Of South African patients entering care during 2016, 23% of men compared to 13% of women had a CD4 count <100 cells/mm^3,[17] while in Zimbabwe in 2015, men were 2.8 times more likely to present to care with a CD4 count <200 cells/mm^3 or WHO stage III or IV disease.[26]

Men may have delays in achieving several stages of the HIV care cascade. A number of studies from SSA report that men are less often tested for HIV.[38-40] For example, in a household-based community survey in South Africa during 2014 to 2015, 65% of women and only 52% of HIV-positive men knew their status.[39] Data from a study of over 14 000 PLWH in 16 SSA countries found that men were consistently less likely to have been tested for HIV.[40] This might in part reflect greater opportunities for testing among women who access clinical sites including antenatal care, but other factors including accessibility and acceptability of testing services for men should also be considered. Men may be less likely to be tested because of anticipated community-level stigma and psychological implications of a positive test result.[41,42] Strategies such as couples-oriented posttest HIV counseling and home-based self-testing are examples of ways to improve men's knowledge of their HIV status.[43-45]

In addition to lower testing rates, men diagnosed with HIV may be less likely than women to promptly link to care and begin ART treatment.[46-48] One South African study estimated that the time for 25% of HIV seroconverters to link to care was 1.7 years for females compared to 3.4 years for men.[46] To help address lower levels of ART enrollment in men compared to women,[49] strategies such as peer-delivered linkage case management and same-day ART initiation are being implemented to reduce time between HIV testing and treatment.[50] To help improve linkage to care, use of "men-oriented" clinical health

services may be perceived as more welcoming and acceptable to males diagnosed with HIV.[44]

This analysis has several limitations. Although we believe our high participation rate and recruitment strategy at 32 diverse sites helped ensure good representation with respect to our target population (HIV-positive patients new to care in SNNPR), specific results from this primarily rural Ethiopian region may differ from those in other regions and countries. However, as noted, our overall conclusions concerning gender differences for presentation with advanced HIV disease, particularly in SSA, are consistent with many other studies. Second, although we have identified men as significantly more likely to present to HIV care with symptoms and advanced disease, specific reasons for this later presentation are unclear. We hypothesize several steps in the HIV care cascade where men may lag behind women, but additional qualitative and quantitative studies are needed to best understand potential barriers at each of these stages. Finally, 240 (13%) of participants in this analysis had either WHO stage I/II disease or a CD4 count >200 cells/mm^3, but not both, making us unable to determine whether or not they had advanced HIV disease. However, the proportion of those with missing data was similar for men and women.

With greater implementation of strategies to promote HIV testing plus immediate and universal initiation of ART and other HIV care, over time the proportion of PLWH who present with advanced disease, including in SSA, should decrease. It is important to continue to monitor these trends, including identification of subpopulations most likely to present with advanced disease. Given our findings and other concordant research, a high priority will continue to be implementation and evaluation of innovative strategies to ensure that all HIV-positive persons, including men, engage in care and initiate treatment as early as possible to help them remain healthy and disease-free.

Ethics

All participants provided informed consent. All data collection forms included only the participant identification number; no personal identifiers were recorded. Approval was obtained from the University of Minnesota's institutional review board (study number 1410S54203) and the Ethiopian Ministry of Science and Technology National Research Ethics Committee (reference number 310/876/07).

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References

1. UNAIDS: Global AIDS update, 2018. Miles to go: closing gaps, breaking barriers, righting injustices. 2018. www.unaids.org/en/resources/documents/2018/global-aids-update. Accessed November 26, 2018.
2. Palella FJ Jr, Armon C, Chmiel JS, et al. CD4 cell count at initiation of ART, long-term likelihood of achieving CD4 >750 cells/mm^3 and mortality risk. *J Antimicrob Chemother*. 2016;71(9):2654–2662.
3. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795–807.
4. TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808–822.
5. Jain V, Hartogensis W, Bacchetti P, et al. Antiretroviral therapy initiated within 6 months of HIV infection is associated with lower T-cell activation and smaller HIV reservoir size. *J Infect Dis*. 2013;208(8):1202–1211.
6. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. *PLoS One*. 2012;7(9):e44454.
7. Baker JV, Sharma S, Grund B, et al. Systemic inflammation, coagulation, and clinical risk in the START trial. *Open Forum Infect Dis*. 2017;4(4):ofx262.
8. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218–230.
9. Okulicz JF, Le TD, Agan BK, et al. Influence of the timing of antiretroviral therapy on the potential for normalization of immune status in human immunodeficiency virus 1-infected individuals. *JAMA Intern Med*. 2015;175(1):88–99.
10. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830–839.
11. Panel on treatment of pregnant women with HIV infection and prevention of perinatal transmission. Recommendations for use of antiretroviral drugs in transmission in the United States. 2018. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Updated May 30, 2018. Accessed November 26, 2018.
12. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services.

2018. www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed October 25, 2018.
13. World Health Organization. *Guidelines for Managing Advanced HIV Disease and Rapid Initiation of Antiretroviral Therapy, July 2017*. Geneva, Switzerland: World Health Organization; 2017. www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en. Accessed November 26, 2018.
14. IeDEA and COHERE Cohort Collaborations. Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs. *Clin Infect Dis*. 2018;66(6): 893–903.
15. Siedner MJ, Ng CK, Bassett IV, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: a meta-analysis. *Clin Infect Dis*. 2015;60(7):1120–1127.
16. Lahuerta M, Wu Y, Hoffman S, et al. Advanced HIV disease at entry into HIV care and initiation of antiretroviral therapy during 2006–2011: findings from four sub-Saharan African countries. *Clin Infect Dis*. 2014;58(3):432–441.
17. Carmona S, Bor J, Nattey C, et al. Persistent high burden of advanced HIV disease among patients seeking care in South Africa's National HIV program: data from a nationwide laboratory cohort. *Clin Infect Dis*. 2018;66(suppl 2):S111–S117.
18. Drain PK, Losina E, Parker G, et al. Risk factors for late-stage HIV disease presentation at initial HIV diagnosis in Durban, South Africa. *PLoS One*. 2013;8(1):e55305.
19. Auld AF, Shiraishi RW, Oboho I, et al. Trends in prevalence of advanced HIV disease at antiretroviral therapy enrollment—10 countries, 2004–2015. *Morb Mortal Wkly Rep*. 2017;66(21): 558–563.
20. Gesesew HA, Ward P, Woldemichael K, Mwanri L. Late presentation for HIV care in Southwest Ethiopia in 2003-2015: prevalence, trend, outcomes and risk factors. *BMC Infect Dis*. 2018; 18(1):59.
21. Nash D, Tymejczyk O, Gadisa T, et al. Factors associated with initiation of antiretroviral therapy in the advanced stages of HIV infection in six Ethiopian HIV clinics, 2012 to 2013. *J Int AIDS Soc*. 2016;19(1):20637.
22. Yendewa GA, Poveda E, Lakoh S, et al. High prevalence of late-stage disease in newly diagnosed human immunodeficiency virus patients in Sierra Leone. *Open Forum Infect Dis*. 2018;5(9): ofy208.
23. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS: progress towards the 90-90-90 targets. Geneva, Switzerland: UNAIDS; 2017. www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf. Accessed November 26, 2018.
24. Cornell M, Schomaker M, Garone DB, et al. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study. *PLoS Med*. 2012;9(9): e1001304.
25. Osler M, Hilderbrand K, Goemaere E, et al. The continuing burden of advanced HIV disease over 10 years of increasing antiretroviral therapy coverage in South Africa. *Clin Infect Dis*. 2018; 66(suppl 2): S118–S125.
26. Nyika H, Mugurungi O, Shambira G, et al. Factors associated with late presentation for HIV/AIDS care in Harare City, Zimbabwe, 2015. *BMC Pub Health*. 2016;16:369.
27. Lifson AR, Workneh S, Hailemichael A, et al. A multi-site community randomized trial of community health workers to provide counseling and support for patients newly entering HIV care in rural Ethiopia: study design and baseline implementation. *HIV Clin Trials*. 2018;19(3):112–119.
28. Federal HIV/AIDS Prevention and Control Office. *HIV/AIDS Strategic Plan: 2015–2020 in an Investment Case Approach, December 2014*. Addis Ababa, Ethiopia: Ethiopian Ministry of Health; 2014. https://hivhealthclearinghouse.unesco.org/sites/default/files/resources/22292.pdf. Accessed December 5. 2018.
29. Fox MP, Rosen S. Retention of adult patients on antiretroviral therapy in low- and middle-income countries: systematic review and meta-analysis 2008–2013. *J Acquir Immune Defic Syndr*. 2015;69(1):98–108.
30. Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma, with particular reference to bronchogenic carcinoma. *Cancer*. 1948;1(4):634–656.
31. World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. Geneva, Switzerland: World Health Organization; 2007. www.who.int/iris/handle/10665/43699. Accessed November 28, 2018.
32. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;163(3): 199–200.
33. Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data, 2017. Geneva, Switzerland: World Health Organization; 2017. www.unaids.org/en/resources/documents/2017/2017_data_book. Accessed November 28, 2018.
34. Assefa Y, Gilks CF, Dean J, et al. Towards achieving the fast-track targets and ending the epidemic of HIV/AIDS in Ethiopia: successes and challenges. *Int J Infect Dis*. 2019;78:57–64.
35. Girum T, Wasie A, Worku A. Trend of HIV/AIDS for the last 26 years and predicting achievement of the 90-90-90 HIV prevention targets by 2020 in Ethiopia: a time series analysis. *BMC Infect Dis*. 2018;18(1):320.
36. UNAIDS. *AIDSinfo, Quick Links, Data Sheet. People living with HIV receiving ART (%), 2017: Ethiopia: Subnational*. (UNAIDS Estimates, Global AIDS Monitoring). 2018. http://aidsinfo.unaids.org. Accessed March 24, 2019.
37. Lifson AR, Demissie W, Ketema K, et al. Failure to test for HIV in rural Ethiopia: knowledge and belief correlates and implications for universal test and treat strategies. *J Int Assoc Providers AIDS Care*. 2013;12(5):306–311.
38. Cherutich P, Kaiser R, Galbraith J, et al. Lack of knowledge of HIV status a major barrier to HIV prevention, care and treatment efforts in Kenya: results from a nationally representative study. *PLoS One*. 2012;7(5):e36797.
39. Grobler A, Cawood C, Khanyile D, Puren A, Kharsany ABM. Progress of UNAIDS 90-90-90 targets in a district in KwaZulu-Natal, South Africa, with high HIV burden, in the HIPSS study: a

household-based complex multilevel community survey. *Lancet HIV*. 2017;4(11):e505–e513.
40. Staveteig S, Croft TN, Kampa KT, Head SK. Reaching the 'first 90': gaps in coverage of HIV testing among people living with HIV in 16 African countries. *PLoS One*. 2017;12(10):e0186316.
41. Treves-Kagan S, El Ayadi AM, Pettifor A, et al. Gender, HIV testing and stigma: the association of HIV testing behaviors and community-level and individual-level stigma in rural South Africa differ for men and women. *AIDS Behav*. 2017;21(9):2579–2588.
42. Chikovore J, Gillespie N, McGrath N, Orne-Gliemann J, Zuma T; ANRS 12249 TasP Study Group. Men, masculinity, and engagement with treatment as prevention in KwaZulu-Natal, South Africa. *AIDS Care*. 2016;28(suppl 3):74–82.
43. Thirumurthy H, Masters SH, Mavedzenge SN, Maman S, Omanga E, Agot K. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. *Lancet HIV*. 2016;3(6):e266–e274.
44. Kojima N, Klausner JD. Strategies to increase human immunodeficiency virus testing among men to reach UNAIDS 90-90-90 targets. *Clin Infect Dis*. 2018;67(9):1468–1469.
45. Orne-Gliemann J, Balestre E, Tchendjou P, et al. Increasing HIV testing among male partners. *AIDS*. 2013;27(7):1167–1177.
46. Maheu-Giroux M, Tanser F, Boily MC, Pillay D, Joseph SA, Barnighausen T. Determinants of time from HIV infection to linkage-to-care in rural KwaZulu-Natal, South Africa. *AIDS*. 2017;31(7):1017–1024.
47. Geng EH, Bwana MB, Muyindike W, et al. Failure to initiate antiretroviral therapy, loss to follow-up and mortality among HIV-infected patients during the pre-ART period in Uganda. *J Acquir Immune Defic Syndr*. 2013;63(2):e64–e71
48. Genberg BL, Naanyu V, Wachira J, et al. Linkage to and engagement in HIV care in western Kenya: an observational study using population-based estimates from home-based counselling and testing. *Lancet HIV*. 2015;2(1):e20–e26.
49. Auld AF, Shiraishi RW, Mbofana F, et al. Lower levels of antiretroviral therapy enrollment among men with HIV compared with women—12 countries, 2002–2012. *Morb Mortal Wkly Rep*. 2015;64(46):1281–1286.
50. MacKellar D, Williams D, Bhembe B, et al. Peer-delivered linkage case management and same-day ART initiation for men and young persons with HIV infection—Eswatini, 2015–2017. *Morb Mortal Wkly Rep*. 2018;67(23):663–667.