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Immunological failure in HIV-infected adults from 2003 to 2015 in Southwest Ethiopia: a retrospective cohort study

Hailay Abrha Gesesew,[1,2] Paul Ward,[1] Kifle Woldemichael,[2] Lillian Mwanri[1]

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[1]Public Health, Flinders University, Adelaide, South Australia, Australia
[2]Epidemiology, Jimma University, Jimma, Ethiopia

Correspondence to
Mr. Hailay Abrha Gesesew; hailushepi@gmail.com

ABSTRACT

Objective To assess the prevalence, trend and associated factors for immunological failure (IF), and the magnitude of antiretroviral therapy (ART) shift among adults infected with HIV in Southwest Ethiopia.

Setting A retrospective cohort study was undertaken using the data from ART clinic at Jimma University Teaching Hospital from 21 June 2003 to 15 March 2015.

Participants Retrospective analysis of 4900 HIV-infected adult patient records dating from June 2003 to March 2015 was conducted.

Primary outcome measure The primary outcome was IF defined when cluster for differentiation 4 (CD4) count falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm^3 after 6 months of ART treatment. The analyses included descriptive and inferential statistics.

Results 546 (19.5%) adults had developed clinical failure (CF), 775 (19.7%) adults had developed IF and 1231 (25.1%) had developed either CF or IF or both. The prevalence of IF was consistently high throughout the decade. Age 25 to ≤50 years adjusted OR (AOR 1.5, 9% CI 1.2 to 2.4), being female (AOR 1.8, 95% CI 1.3 to 1.9), late presenter for HIV care (AOR 2.2, 95% CI 1.6 to 2.7) and having baseline CD4 count below 200 cells/mm^3 (AOR 5.5, 95% CI 4.1 to 7.4), and having no history of HIV testing before diagnosis (AOR 0.7, 95% CI 0.5 to 0.9) were the predictors for IF. Only 29 (0.9%) adults infected with HIV were shifted to second-line ART regimen.

Conclusions The magnitude of CF or IF or both was found significant and consistently high throughout the calendar year although ART shift was found minimal. HIV-infected adult patients with IF were early age adults, females, late presenters for HIV care, and those who had low baseline CD4 counts and history of HIV testing before diagnosis.

Strengths and limitations of this study

- The study included 12-year retrospective follow-up, and had involved large sample size bigger than several other similar studies.
- The study assessed the outcomes of immunological failure, and this was not studied so far.
- The source of the data was a record based and could have incompleteness.
- The context of treatment failure attributed to immunological and/or clinical failure could be a spuriously biased estimate.
- The findings may not infer to another level of health institutions such as health centres or private hospitals.

INTRODUCTION

The advent of highly active antiretroviral therapy (ART) since 1996 has significantly reduced HIV-related diseases, improved quality of life of patients with HIV and decreased deaths associated with HIV.[1 2] Even though the ART is scaled up worldwide, the coverage is still low. As of 2015, the majority of countries had low (<50%) ART coverage, few countries had moderate (50%–80%) and none had high (>80%) coverage.[2 3] The estimated global ART coverage in 2015 was low (40.6%), of which North Africa and Middle East had the lowest coverage (19%) and high-income countries had the highest (67%).[2] Sub-Saharan Africa (SSA) had also low ART coverage (42.35%) in 2015 and Ethiopia, one of the countries in SSA, had 51.9% coverage.[2] The impediments in the ART programmes are not limited to the issue of coverage. A substantial number of patients had developed immunological,[4–7] clinical failure (CF)[5 8 9] and/or treatment failure (TF).

Immunological failure (IF) was considered as a surrogate marker for virological failure.[10 11] Thus, IF vividly influences the performance of a virological suppression goal of the UNAIDS (Joint United Nations Programme on HIV and AIDS) 90-90-90 targets[12] that aimed at achieving 90% of the virological success of patients on ART. Research has reported an IF magnitude of 23%–33.1% in Europe,[13] 9%–18% in Asia[14 15] and 11%–39% in Africa.[16] In Ethiopia, few studies have assessed IF[4 6 7 17] and reported a prevalence of 6.8%–21%. The above studies presented the following risk factors, but not limited to: unemployment, low baseline cluster for differentiation 4 (CD4) cell, baseline WHO clinical stage 4, poor adherence to treatment, not disclosing HIV status and

development of new opportunistic infection (OI) after starting treatment.

However, all the studies that assessed the prevalence and risk factors of IF[4 6 7 17 18] were conducted in the settings where the prevalence of HIV was below 2%. Jimma—the current study setting—is near Gambella region (Southwest Ethiopia), a region known to have the maximum prevalence rate (6.5%) of HIV in Ethiopia.[19] The hospital serves both Jimma and Gambella zones. Since the prevalence of HIV in Southwestern region is higher (6.5%) than other parts of the nation (<2%), it is essential to comprehend whether the high prevalence is linked with other factors than the ones reported in similar studies in Ethiopia. In addition, unlike the rest of Ethiopia, the Southwest region is composed of diverse population groups. A substantial number of HIV-infected patients enrolled in the ART clinic in Jimma University Teaching Hospital (JUTH) come from a refugee camp situated near Jimma, which hosts refugees from different East African countries.

The exposure of ART—if not taken according to the recommendations—leads to drug resistance and subsequent clinical and/or IF. Therefore, timely switching to alternatives (second-line or third-line drugs) is immensely needed.[20] Late shifting of regimens further increases the risk of viral resistance and endangers the long-term prognosis.[20] ART switch is less common in under-resourced settings than in resourced countries.[21] In Ethiopia, the magnitude of shifting to second-line ART drugs due to TF attributed to IF and/or CF has not been assessed. Furthermore, the trend and outcomes across the immunological status of HIV-infected adults in Ethiopia is yet to be addressed. Hence, it is crucial to explore IF contextually. The performance assessment of virological suppression of the UNAIDS 90-90-90 treatment targets was also never assessed in the nation. We performed a historical data analysis to assess the prevalence, trend, outcomes and associated factors of IF, and the magnitude of shifting to second-line ART drugs among adults in Southwest Ethiopia.

METHODS

Study design, setting and participants

A retrospective cohort study was carried out using data from 21 June 2003 to 15 March 2015 from the ART clinic at JUTH. We have described the study setting elsewhere.[22 23] The target population included all HIV-infected adult patients age ≥15 years enrolled in ART care at JUTH in Southwest Ethiopia. Patients should be followed for at least 6 months after ART initiation. If the CD4 level or WHO clinical stage of the patients was not recorded, at least, at two points—beginning and after 6 months of ART initiation—records would be excluded from the analysis. Baseline refers the time when ART was started for the first time.

Data source and procedures

Data were extracted from JUTH electronic medical records (EMRs) system called comprehensive care centre patient application database (C-PAD). This system was designed in 2007, and data recorded before 2007 were retrospectively copied from the paper in to the EMR system. In 2003–2015, 4900 adults were on ART out of 8172 HIV-infected patients in the care, and 3939 (81%) of them were included in the analysis for IF (figure 1). Health workers record the clinical and non-clinical characteristics of the patients on a paper followed by entering into the EMR by data clerks. To ensure completeness, reliability and validity of the information, two data clerks enter the data. In addition, International Center for AIDS Care and Support at Colombia University assists the patient-level data management system.

Study variables and measurements

WHO[24] has set definitions for IF, CF and TF. The response variable was IF and dichotomised as yes and no. IF (yes) was defined if CD4 count of the HIV-infected adults falls to the baseline (or below) or persistent CD4 levels below 100 cells/mm^3 after 6 months of ART treatment.[24] The independent variables included age, sex, marital status, educational status, religion, ART adherence, cotrimoxazole adherence, baseline WHO clinical staging, baseline CD4 count, late presentation for HIV care, tuberculosis (TB)/HIV coinfection, baseline functional status, history of HIV testing before diagnosis and ART shift. CF was defined when new or recurrent clinical conditions denoting WHO clinical stage 4 6 months after an effective treatment.[24] TF refers to a combination of CF and IF. ART discontinuation was either loss to follow-up (LTFU), defaulting and/or stopping medication while remaining in care. LTFU was defined when patients had been on ART treatment and missed at least three clinical appointments but not yet been classified as 'dead' or 'transferred out' (TO). Defaulting was defined when patients had been on ART treatment and missed less than three clinical appointments but not yet been classified as 'dead' or 'TO'. In addition, stopping medication was defined when patients had stopped treatment due to any reason while they have remained in care. TO is the official transferring of the patient to another ART clinic. Functional status was categorised in to work (able to perform usual work), ambulatory (able to perform activity of daily living) and bedridden (not able to perform activity of daily living). ART switching is a change from first-line to second-line ART drugs. History of HIV testing refers to testing (one or more times) for HIV before diagnosis. Table 1 demonstrates the measurements of late presentation for HIV care and level of adherence. If poor HIV outcomes such as IF, CF and TF were occurred more than once, the latest outcome was considered for analysis. The assessment for other outcomes such as discontinuation, adherence and ART shift was conducted at the end of follow-up time.

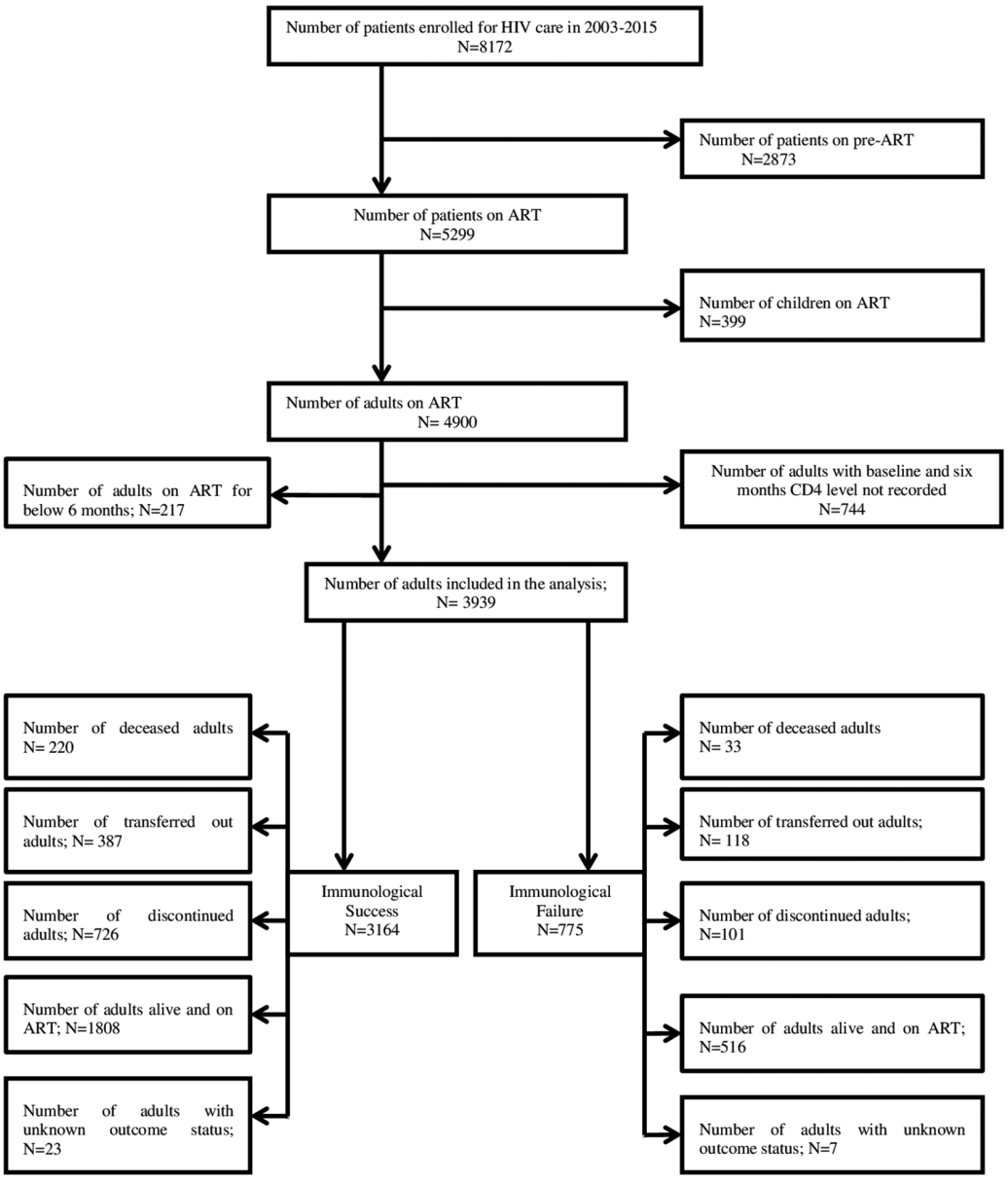

Figure 1 Immunological status and their outcomes of HIV-infected adults in Jimma University Teaching Hospital in Southwest Ethiopia, 2003–2015. This figure presents the flow chart of immunological status and their outcomes of HIV-infected adults. ART, antiretroviral therapy; CD4, cluster for differentiation 4.

Statistical analyses

We undertook the analysis of descriptive and inferential statistics. Descriptive statistics included frequency tables and proportions for categorical data, and median, range and line graph for continuous data. The 10-year trends for IF (data for years 2003 and 2015 were excluded since the number of months was incomplete) was described by line graph using a cumulative frequency percentage. The cumulative frequency percentage or proportion of patients with IF, denoted in Y-axis in figure 2, is calculated using the cumulative number of patients with IF (cumulative frequency for numerator) and eligible cumulative number of patients for IF (cumulative frequency for denominator) for each calendar year. Binary logistic regression was applied to assess factors associated with IF. Bivariate logistic regression analysis was performed to select the candidate variables to multiple logistic regression, and variables with $p<0.25$ were included as candidate variables to multivariable logistic regression. $P\leq0.05$ was considered a criterion for statistical significance in the final model. We performed multiple imputations (MIs) (n=5) assuming missing at random (MAR) pattern[25] to treat missing data, and we reported a model with pooled imputed values.[26] We used Hosmer and Lemeshow test to check goodness of fit of the final model. We summarised the data using OR and 95% CI. We used SPSS V.22.0 for all data analyses.

Patient and public involvement

We did not involve patients and public in the study—we simply extracted data from records.

Table 1 Measurements for late presentation for HIV care and ART adherence, 2016

Late presentation for HIV care*[53]	
Enrolled in 2003–2011	**Enrolled in 2012–2015**
CD4 lymphocyte count of <200 cells/µL irrespective of WHO clinical stage at the time of first presentation to the HIV care.	CD4 lymphocyte count of <350 cells/µL irrespective of WHO clinical stage at the time of first presentation to the HIV care.
WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care.†	WHO clinical stage 3 or 4 irrespective of CD4 count at the time of first presentation to the HIV care.†

Level of adherence‡[54]			
Status	**Percentage of prescribed ART intake**	**No of missing doses out of 30**	**No of missing doses out of 60**
Good	≥95%	<3	<4
Fair	85%–95%	3–5	4–9
Poor	<85	≥6	≥9

*The definition for late presentation for HIV care among TB/HIV-coinfected population was only based on the CD4 criteria.[22]
†WHO clinical stage 3 was defined if one of the following is present in an HIV-diagnosed patient: weight loss of >10% body weight, chronic diarrhoea for >1 month, fever for >1 month, oral candidiasis, oral hairy leukoplakia or pulmonary TB within the previous year or severe bacterial infections; WHO clinical stage 4 was defined if one of the following is present in an HIV-diagnosed patient: HIV wasting syndrome, PCP (Pneumocystis carinii pneumonia), toxoplasmosis of the brain, cryptosporidiosis or isosporiasis with diarrhoea for >1 month, cytomegalovirus disease of an organ other than liver, spleen or lymph node, herpes simplex virus infection, progressive multifocal leucoencephalopathy, candidiasis, extrapulmonary TB, lymphoma, Kaposi's sarcoma, HIV encephalopathy.
‡Clinicians and pharmacists ask patients and check the pill container to collect the number of missing doses or day.
ART/ARV, antiretroviral therapy; CD4, cluster for differentiation 4; TB, tuberculosis.

RESULTS

Description of study participants

In total, 8172 patients were enrolled in HIV care programme from 21 June 2003 to 15 March 2015 of whom 4900 adult patients had been documented commencement of ART (figure 1). demonstrates the characteristics of adult patients with HIV on ART. Of 4900 HIV-infected patients on ART, four out of five were aged 25–50 years, three out of five were females, one out of two were married, two out of three were Christians and two out of five completed primary education. The median CD4 count was 156 (0–1313) cells/mm3, and more than half (54.3%) of the participants had baseline WHO clinical stage 3 or 4. The magnitude of TB/HIV coinfection over the study period was 27.9%. The median time on ART was 49 months, and the estimated survival time was 121.9 (120.3–123.5) months.

IF, CF and ART regimen switching

Of the 4900 patients enrolled on ART in 2003–2015, 217 patients were on ART for below 6 months, and baseline and 6 months CD4 level of 744 patients was not recorded. In total, 775 out of the 3939 patients (19.7%) had developed IF. Out of the patients with IF, 83 (10.7%), 88 (11.3%) and 604 (77.9%) patients, respectively, were followed for 6 to ≤12, 12 to ≤24 and ≥24 months. Among the patients who developed IF, 33 (4.3%) patients had died, 101 (13%) patients had discontinued, 118 (15.2%) patients had TO and 516 (66.6%) were alive and on ART (figure 1). The magnitude of IF was steadily high since 2008 and reached a peak in 2009 accounting for 24% followed by 21% in 2014. Figure 2 shows the trend in IF in HIV-infected patients on ART. In addition, 2807 patients were eligible for CF of whom 546 (19.5%) had developed the CF. A total of 1231 out of 4470 had developed either CF or IF or both—82 patients had both CF and TF. Twenty-nine (0.9%) patients were shifted to second-line ART drugs.

Factors associated with IF among adult patients with HIV

Table 3 demonstrates the outputs from the multivariable logistic regression analysis of factors for IF obtained from the analysis of a complete case and MIs. Age between 25 and ≤50 years, being female, late presenter for HIV care and having a baseline CD4 count below 200 cells/mm^3 were factors for IF, and having no history of HIV testing before diagnosis was a protective factor against IF. HIV-infected adults age 25 to ≤50 years were 50% adjusted OR (AOR 1.5, 9% CI 1.2 to 2.4) more likely to develop IF than those aged 15 to ≤25 years. Females were 80% more likely than males (AOR 1.8, 95% CI 1.3 to 1.9) to develop IF. Patients who presented late for HIV care had double the risk of IF than early presenters (AOR 2.2, 95% CI 1.6 to 2.7). In addition, patients with baseline CD4 count below 200 cells/mm^3 had nearly six times higher risk for IF than those with ≥200 cells/mm^3 (AOR 5.5, 95% CI 4.1 to 7.4). Patients who had no history of HIV testing before diagnosis were 30% less likely (AOR 0.7, 95% CI 0.5 to 0.9) to develop IF as compared with those who had previous record of HIV testing.

Multiple imputations

The MIs analysis result (table 3) revealed that except for baseline CD4 count, all statistically significant variables in the complete case analysis were also reported to have a statically significant difference in the MIs analysis. TB/HIV coinfection, a variable that was not statistically significant in the complete case analysis, was found to be a

Table 2 Characteristics of adult HIV-infected patients enrolled on ART care in Southwest Ethiopia from 2003 to 2015, Jimma, Ethiopia

Variable	n=4900, n (%)
Age in years	
15 to ≤25	711 (14.5)
25 to ≤50	3937 (80.3)
50+	252 (5.2)
Median (range) age in years	30 (15–81)
ART follow-up time in months, median (range)	49 (0–137)
Estimated survival time in months, median (95% CI)	121.9 (120.3 to 123.5)
Sex	
Male	1971 (40.2)
Female	2929 (59.8)
Marital status*	
Never married	897 (20.9)
Married	2094 (48.7)
Separated/divorced/widowed	1311 (30.5)
Education*	
No education	945 (21.9)
Primary	1687 (39.1)
Secondary and above	1685 (39)
Religion*	
Muslim	1402 (32.6)
Christian†	2893 (67.4)
Baseline WHO classification*	
1 or 2	1355 (45.7)
3 or 4	1608 (54.3)
Baseline CD4 count (cells/mm^3)*	
<200	3275 (73.6)
≥200	1174 (26.4)
Median (range)	156 (0–1313)
Hx of TB/HIV coinfection*	
No	3533 (72.1)
Yes	1367 (27.9)
ARV adherence*	
Good	4064 (82.9)
Fair or poor	836 (17.1)
Cotrimoxazole adherence*	
Good	4119 (94.4)
Fair or poor	762 (15.6)
Hx of HIV testing*	
Yes	2860 (58.4)
No	2040 (41.6)
ART shift*	
No	3190 (99.1)
Yes	29 (0.9)
Baseline functional status*	
Work or ambulatory	3064 (68.1)
Bedridden	1437 (31.9)
Timing to HIV diagnosis	
Early	894 (33.3)
Late	1788 (66.7)
Clinical failure*	
No	2261 (80.5)
Yes	546 (19.5)
Immunological failure*	
No	3164 (80.3)
Yes	775 (19.7)
Treatment failure*	
No	3239 (72.5)
Yes	1231 (27.5)

*Only valid percentage is calculated.
†Orthodox, catholic, protestant.
ART/ARV, antiretroviral therapy; CD4, cluster for differentiation 4; TB, tuberculosis.

statistically significant in MIs analysis in which patients with TB/HIV-coinfection had a greater risk of developing IF than patients with HIV alone.

DISCUSSION

The current study was undertaken to assess IF in (and near) high HIV epidemic area and revealed a prevalence rate of 19.7% with a sharp trend increase in the recent times. This prevalence is similar to a finding from a study conducted by Melsew Yayehird *et al*[4] but is higher than the findings of studies conducted in the other part of the nation that was reported to be between 6.7% and 17.6%.[6 7 17]

The result shows that the prevalence rate of IF is significant particularly when compared with the other part of the nation. Thus, we can hypothesise that patients who come from high HIV-prevalence areas or attending their HIV care services near to high HIV-endemic settings has higher IF than patients who are attending their care in or near to low HIV-prevalence settings. The following explanations could partly justify the difference: (1) the presence of variety HIV-1 strains among people living with HIV in HIV prevalent areas is very high and this could challenge the immunological response benefited from the treatment[27 28]; (2) ART drug resistance is higher in high than low HIV-prevalence settings, and the drug resistance diminishes the immunological benefit of the treatment[29] and (3) HIV-infected people who come from high HIV-prevalence settings have less access to health services, lower economic status and lower HIV care-related knowledge[30] and this could negatively influence the immunological benefit of ART. For instance,

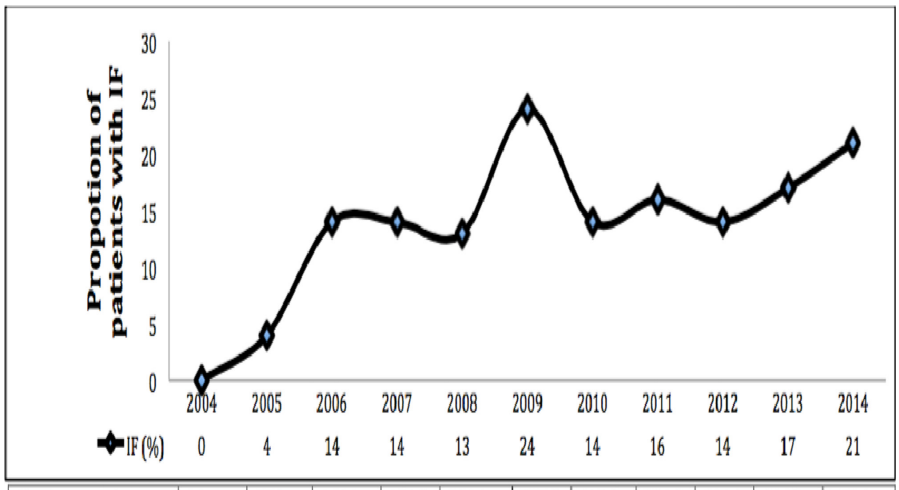

Figure 2 Trends in the percentage distribution of IF in HIV-infected adults on ART, Southwest Ethiopia, 2004–2014. This figure presents the trend of IF. Y-axis shows the cumulative frequency percentage of patients with IF for each calendar year. ART, antiretroviral therapy; IF, immunological failure.

the 2016 Ethiopian Demographic Health Survey ([31] stated that two-thirds (66%) of Tigray (a regional state located in Northern Ethiopia) women versus less than half (43.9%) of Gambella (a regional state located in Southwest Ethiopia) women stated that HIV can be prevented by using condoms and limiting sexual intercourse to one uninfected partner. Similarly, this survey described that more than three-fourths (84.2%) of Tigray men versus two-thirds (69.2%) of Gambella men stated that HIV can be prevented by using condoms and limiting sexual intercourse to one uninfected partner. Therefore, intensive effort has to be done to reduce the IF and subsequently a virological failure.

In the current study, most patients (78%) with IF were followed in ART care for ≥2 years. This shows that the prevalence of IF grows when the follow-up time increases, and this was similar to the previous studies conducted elsewhere.[4 8] The relationship between longer duration of treatment and IF could be justified by multiple explanations, and needs further study. But it may be partly justified by the frequent (and inappropriate) change in dose or types of ART, non-adherence when patients are on ART for long periods and ART resistance.[8 9] Thus, long-term retention requires serious attention. Plasma HIV-1 RNA is not available for routine viral load monitoring in resource-limited countries such as Ethiopia.[18] Hence, WHO[32] and several other studies[10 11 33] recommended immunological success as a surrogate marker for the virological suppression. In the current study, 19.7% of patients had IF; said in another way, 80.3% of patients had immunological success. This 80% (even lower) performance of virological suppression is less than the current goal of virological suppress of the UNAIDS 90-90-90 target that aimed 90% viral suppression for those on treatment.[12] Nevertheless, as the predictive accuracy is low, immunological success overestimates virological suppression.[34 35] Therefore, plasma HIV viral load testing should be accessible to regularly monitor the patients. The use of GenXpert for HIV viral load testing[36] is also another option for resource-limited countries.

HIV-infected patients with IF were more likely to be between 25 and ≤50 years of age, females, late presenters for HIV care, and those who had low baseline CD4 counts and history of HIV testing before diagnosis. Age was reported to have a significant influence on probability of IF. In fact, other literatures[37 38] reported that older adults are more likely to develop IF than younger group. The impairment in immune recovery due to age-related reduction in thymic function and other regenerative mechanisms could justify the link between older adults and IF.[38] Older adults are also highly likely to be diagnosed late with HIV than the younger ones,[39] a phenomenon that prevents an immunological benefit from ART.[40] Even though, majority of the literatures[41–43] reported no statistical difference between sex and IF, the proportion in the current study and one other study[16] revealed that females were more likely to develop IF than males. In the present study, females were the majority of the study participants. This shows that females are still the vulnerable groups, and are at a greater risk of negative HIV care outcomes. This could be attributed to high levels of stigma,[44 45] low literacy status[46] and use of traditional medicine.[47] Thus, attention has to be given for females in each series of the cascade of care.

Similar to findings from other studies,[16 48] low baseline CD4 counts were linked with IF. Furthermore, late presenters for HIV care had a greater risk of IF than early presenters, and this finding was supported by findings from studies conducted in SSA.[49 50] Research has shown that delayed presenter and patients with low baseline

Table 3 Logistic regression findings of factors affecting IF in patients with HIV infection, 2003–2015, Jimma, Ethiopia

Variable	IF (n, %†)		COR (95% CI)	AOR (95% CI): complete cases	AOR (95% CI): multiple imputations
	No	Yes			
Age (years)					
15 to ≤25	488 (15.4)	74 (9.5)	1	1	1
25 to ≤50	2560 (80.9)	674 (87)	1.7 (1.3 to 2.3)*	1.5 (1.2 to 2.4)*	1.8 (1.7 to 2.1)*
50+	116 (3.7)	27 (3.5)	1.5 (0.9 to 2.5)	1.3 (0.7 to 2.9)	2.3 (1.9 to 2.7)*
Sex					
Male	1488 (47)	274 (35.4)	1	1	1
Female	1676 (53)	501 (64.6)	1.6 (1.4 to 1.9)*	1.8 (1.3 to 1.9)*	1.7 (1.6 to 1.8)*
Marital status					
Never married	632 (23.3)	152 (21.7)	1		1
Married	1316 (48.5)	357 (51.1)	1.1 (0.9 to 1.4)		1.04 (0.0 to 1.1)
Separated/divorced/ widowed	766 (28.2)	190 (27.2)	1.03 (0.8 to 1.3)		1.9 (0.7 to 2.1)
Educational status					
No education	559 (20.5)	145 (20.8)	1	1	1
Primary	1089 (39.9)	287 (41.1)	1.01 (0.8 to 1.3)	1.3 (0.7 to 2.9)	1.03 (0.9 to 1.1)
Secondary and above	1084 (39.7)	266 (38.1)	0.9 (0.8 to 1.2)	0.7 (0.4 to 3.7)	0.9 (0.8 to 1.1)
Religion					
Muslim	871 (32)	239 (34.5)	1		1
Christian‡	1849 (68)	453 (65.5)	0.9 (0.8 to 1.06)		0.8 (0.7 to 1.9)
Baseline WHO status					
Stage 1 or 2	842 (45.1)	216 (46.6)	1	1	
Stage 3 or 4	1027 (54.9)	248 (53.4)	0.9 (0.8 to 1.2)	1.7 (0.8 to 3.9)	
Baseline CD4					
≥200 cells/μL	2558 (80.8)	350 (45.2)	1	1	1
<200 cells/μL	606 (19.2)	425 (54.8)	5.1 (4.3 to 6.06)*	5.5 (4.1 to 7.4)*	1.8 (0.9 to 3.01)
Clinical failure					
No	1493 (81.3)	352 (80.5)	1	1	1
Yes	343 (18.7)	85 (19.5)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	2.8 (0.7 to 4.9)
HIV care presentation					
Early	682 (36.5)	99 (21.3)	1	1	1
Late	1187 (63.5)	365 (78.7)	2.1 (1.7 to 2.7)*	2.2 (1.6 to 2.7)*	1.1 (1.01 to 1.2)*
Hx of TB/HIV coinfection					
No	2229 (70.4)	536 (69.2)	1	1	1
Yes	935 (29.6)	239 (30.8)	1.06 (0.9 to 1.3)	1.8 (0.7 to 4.9)	1.08 (1.01 to 1.2)*
ART adherence					
Good	2595 (82)	648 (83.6)	1		1
Fair or poor	569 (18)	127 (16.4)	0.9 (0.7 to 1.1)		0.9 (0.8 to 1.9)
Cotrimoxazole adherence					
Good	2632 (83.5)	639 (82.5)	1		
Fair or poor	521 (16.5)	136 (17.5)	0.9 (0.8 to 1.2)		
Baseline functional status					
Working or ambulatory	1992 (68.1)	549 (74.7)	1	1	
Bedridden	933 (31.9)	186 (25.3)	0.7 (0.6 to 0.9)*	0.8 (0.6 to 1.02)	
Hx of HIV testing					
Yes	1793 (56.7)	468 (60.4)	1	1	1
No	1371 (43.3)	307 (39.6)	0.9 (0.7 to 1.0)	0.7 (0.5 to 0.9)*	0.8 (0.7 to 0.9)*

Continued

Table 3 Continued

Variable	IF (n, %†) No	IF (n, %†) Yes	COR (95% CI)	AOR (95% CI): complete cases	AOR (95% CI): multiple imputations
ART shift					
No	2086 (98.9)	500 (99.2)	1		1
Yes	24 (1.1)	4 (0.8)	0.7 (0.2 to 2.01)		0.8 (0.6 to 1.03)

*Statistically significant at p≤0.05.
†Only valid percentage is considered.
‡Orthodox, protestant or catholic.
AOR, adjusted OR; ART, antiretroviral therapy; CD4, cluster for differentiation 4; COR, crude OR; IF, immunological failure; TB, tuberculosis.

CD4 counts are at an elevated risk for OIs and multiple comorbidities.[51] This prevents patients from taking the treatment consistently and gaining the immunological benefit.[40] Frequent screening and opt-out testing would normalise HIV testing, reduce stigma associated with HIV care and help those infected with HIV find out earlier.[52]

Finally, people who had history of HIV testing before diagnosis were less likely to gain an immunological response compared with those who had not. This might be justified by the fact that those who had history of HIV testing before diagnosis and once got HIV-negative result might feel sense of well-being and get tested late. Thus, the delayed HIV diagnosis and then delayed presentation to ART care could challenge the immunological gain from ART.[40] However, it is interesting that ART adherence was not statistically associated with IF, and this needs further research. Out of the 775 patients who developed IF or 546 patients who developed CF, only 29 adults switched to second-line ART drugs. This shows that the great majority of patients diagnosed with TF attributing to IF and/or CF were not moved onto second-line therapy.

The study has some limitations: (1) the retrospective nature of the study does not assure the cause–effect relationship as some of the variables could be measured after the occurrence of the outcome; (2) the possibility of having incomplete information could reduce the precision of estimates for the included variables; nonetheless, we have addressed this using MIs; (3) the source of information—being from public referral hospital—may not infer to another level of health institutions such as health centres or private hospitals; (4) the lack of viral load to detect TF is another limitation and (5) while including the latest episode of a poor outcome in an analysis of predictors, factors associated with first poor outcome may be different from factors associated to a poor outcome in a person who has already been on ART for several years and experienced multiple previous poor outcomes. Furthermore, we are unable to extract some data prior to each episode of IF to conduct further analyses, and explicitly identify associated factors for each episode.

CONCLUSIONS

In conclusion, the 19.7% prevalence of IF is higher in or near high HIV-prevalence settings—the current study setting—than low HIV-prevalence settings in Ethiopia that reported an IF prevalence of 6.7%–17.6%. However, great majority of the associated factors from the current study are incongruent to the findings of previous studies conducted in the country and elsewhere. Patients with IF were more likely to be early age adults, females, late presenters for HIV care, and have a low (<200 cells/mm^3) baseline CD4 count and history of HIV testing before diagnosis. Very few patients were shifted to second-line ART drugs despite the high prevalence of CF and/or IF. Research has shown that delayed ART regimen switching increases the risk of viral resistance and endangers the long-term prognosis of HIV-infected patients on ART. Hence, to further improve immunological response of the patients, benchmarking practices and effective programmes should be developed to diagnose and link HIV-infected patients timely, improve retention care and increase the regular immunological and virological monitoring of the patients.

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