HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2019 January 28.

Published in final edited form as:

AIDS. 2018 January 28; 32(3): 363–369. doi:10.1097/QAD.0000000000001706.

The validity of self-reported antiretroviral use in persons living with HIV: a population-based study

M.K. Grabowski[1,2,3], **S.J. Reynolds**[2,4,5], **J. Kagaayi**[2], **R.H. Gray**[1,2], **W. Clarke**[5], **L.C. Chang**[2,5,6], **G. Nakigozi**[2], **O. Laeyendecker**[1,4,5], **A.D. Redd**[4,5], **V. Goud-Billoux**[1], **R. Ssekubugu**[2], **F. Nalugoda**[2], **M.J. Wawer**[1,2], **D. Serwadda**[2,7], **T.C. Quinn**[2,4,5], and **A.A.R. Tobian**[1,2,3]

[1]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland [2]Rakai Health Sciences Program, Entebbe, Uganda [3]Department of Pathology, School of Medicine, Johns Hopkins University, Baltimore, Maryland [4]Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA [5]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland [6]Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland [7]School of Public Health, Makerere University, Kampala, Uganda

Abstract

Objective—To assess the validity of self-reported antiretroviral therapy use (ART) using population-based cohort data.

Methods—Self-reported ART use and non-use was compared to a validated laboratory assay in 557 HIV-positive participants in the Rakai Community Cohort Study surveyed between September and December 2011 in Rakai, Uganda. The study population included participants from seven communities, including one fishing community with high HIV prevalence (~41%). ART use was assayed using liquid chromatography-tandem mass spectrometry which detects 20 antiretroviral (ARV) drugs. HIV viral load measurements were also obtained. Individuals with ≥2 antiretroviral (ARV) drugs detected were considered to be using ART.

Results—153 (27%) participants self-reported ART use of whom 148 (97%) had ≥2 ARV drugs detected. There were ≥2 ARV drugs detected in 11% (n=44/404) of individuals with no self-reported ART use. Overall, the specificity of self-reported ART use was 99% (95%CI:97–100%) and the sensitivity was 77% (70–83%). Positive and negative predictive values were 97% (95%CI: 93–99%) and 89% (95%CI: 86–92%), respectively. Non-disclosure of ART use was significantly more common in younger persons (<30 years) and among those in trading occupations, but did not vary by community of residence.

Conclusions—Self-reported ART use has high specificity and moderate sensitivity providing reasonable, but conservative estimates of population-based ART use. There is more under-

Corresponding Author: Mary K. Grabowski, Ph.D., Department of Pathology, Johns Hopkins University, 446 Room C, Carnegie Building, 600 N. Wolfe St., Baltimore, MD 21205, 410-614-7386, mgrabow2@jhu.edu.

reporting of ART use among younger persons and traders suggesting a need for more research on barriers to self-reporting of ART use in these sub-groups.

Keywords

AIDS; HIV; antiretroviral therapy; combination HIV prevention; self-report; validity; Uganda; Sub-Saharan Africa

INTRODUCTION

Antiretroviral therapy (ART) is being rapidly scaled in Sub-Saharan Africa to reduce HIV-related mortality and new HIV transmissions [1–3]. Accurate measurement of population-level ART use is needed to evaluate these programmatic efforts. ART reduces plasma HIV viral load, a quantitative measure of replicating virus in the blood [2, 4]. Community HIV viral load suppression, defined as the proportion the HIV-positive persons in a community with a suppressed viral load, is a common measure of ART effects in populations, but limited resources and logistics for large-scale viral load testing are barriers to its use in many African settings[5]. Viral load may also misclassify persons if individuals who are using ART have drug resistant virus. Plasma drug monitoring with high performance liquid chromatography (HPLC) detects individual antiretroviral drugs and is considered a gold standard measure of ART use; however, it has been applied sparingly because it requires expensive laboratory equipment and materials and specialized expertise [6–8]. In contrast, self-reported ART use is a simple, efficient and cost-effective method to assess the prevalence of ART use in a population survey, but the validity of population-based self-reported ART use has not been well characterized.

Prior studies have assessed the validity of self-reported ART using plasma HPLC in sub-Saharan Africa predominately within the context of clinical trials including at enrollment and adherence to ART regimens during follow-up [9–13]. Assessments at enrollment have shown that almost half of trial enrollees with undetectable viral loads fail to report ART use when eligibility criteria are restricted to those who have not initiated therapy [9, 10]. Here we assess the validity of self-reported ART use using HPLC as a gold standard in a population-based survey and serum samples from adults aged 15–49 years in Rakai, Uganda. We also measure viral load and assess ART drug resistance.

METHODS

Study population/design

Results of self-reported ART use and non-use were compared to a validated HPLC laboratory assay among HIV-positive participants in the Rakai Community Cohort Study (RCCS). The RCCS, conducted by the Rakai Health Sciences Program, is an open population-based survey of adults, aged 15–49 years, in Rakai District Uganda [14]. To identify eligible participants, the RCCS first holds an informational community mobilization event. This is followed by a household census which enumerates all persons by gender, age, and duration of residence. Individuals must be between the ages of 15–49 and a resident for at least six months in agrarian and trading communities and one month with an intention to

stay longer in fishing communities for inclusion in the RCCS. After the census, the RCCS surveys all present, age-eligible residents providing written informed consent at central community locations referred to as “hubs”. Up to two attempts are made to contact individuals who do not come to the hubs for interview at their household.

Samples and data for this study were collected between September 13, 2011 and December 1, 2011 from 557 HIV-positive RCCS participants residing in seven communities, including one high HIV prevalence fishing community on Lake Victoria (~41% HIV prevalence). HIV prevalence in the other communities was ~13%. At the time this study was initiated, it was conducted using samples from all consenting age-eligible HIV-positive participants in the most recent, ongoing survey. Therefore, the only selection criterion for this validation study was calendar time. The participants tested represented the first 16% of HIV-positive individuals who participated in the RCCS that survey round.

Participants were interviewed to assess demographics, sexual behaviors, and ART use. Specifically, ART use was assessed by first asking participants if they were taking any long-term medications. If participants responded yes to this question, they were then asked if they were taking antiretrovirals. Only participants who responded yes to both questions, were considered to have self-reported ART use. Venous blood was also obtained for HIV testing at time of survey and remaining serum was stored at −80°C for future laboratory testing. The RCCS is approved by the Uganda Virus Research Institute Research and Ethics Committee, the Uganda National Council for Science and Technology, and the Western Institutional Review Board (Olympia, WA).

Laboratory assays

Stored sera was tested to assess HIV viral loads, ART use, and to perform viral sequencing to detect HIV drug resistance. HIV-1 viral load testing was performed using the Abbott RealTime assay (Abbott Molecular, Inc., Des Plaines, IL 60018). For the current study, viral suppression was defined using a cutoff of 400 copies/ml.

Serum samples were analyzed for the presence of 20 antiretroviral (ARV) drugs: six NRTIs (emtricitabine [FTC], tenofovir [TDF], lamivudine [3TC], stavudine, abacavir and zidovudine [ZDV]), three non-nucleoside reverse transcriptase inhibitors (NNRTIs; efavirenz [EFV], rilpivirine and nevirapine [NVP]), and nine protease inhibitors (PIs; atazanavir, amprenavir, darunavir, lopinavir, indinavir [IDV], nelfinavir [NFV], saquinavir [SQV], tipranavir [TPV], and ritonavir [RTV]) also raltegravir and maraviroc[7, 8]. Samples were prepared using Phenomenex Strata-X 96-well SPE plates [Torrance, CA], where the plates were pre-conditioned with 200 uL of methanol, 200 uL of internal standard mix (abacavir-d4 and lopinavir d-8) in aqueous solution with 1% trifluoroacetic acid/0.025% formic acid was added, followed by addition of plasma sample. Each well was washed with 200 uL of water (eluent discarded), followed by 2 washes with methanol, where the eluent was collected and saved for analysis. ARV drugs were detected with a modified version of a previously published assay using high-performance liquid chromatography (HPLC) coupled with high-resolution accurate mass (HRAM) mass spectrometry (MS; QExactive; Thermo Fisher Scientific, San Jose, CA) [8]. The mobile phase system consisted of 10 mM ammonium formate and formic acid (0.05%) and methanol with 0.05% formic acid. Samples

were introduced onto a 1.9-μm Hypersil Gold perfluorinated phenyl column at 100% aqueous composition; elution occurred during a 2.5 minute step-and-hold isocratic step to 100% methanol. Presence of drugs was detected using targeted tandem mass spectrometry, where the precursor ion was selected at nominal mass using the quadrupole, and fragments were analyzed at high resolution using the orbitrap. All ions were detected in the positive mode, with resolution of 17,500 at a mass to charge ratio of 200. The limit of identification for all ARV drugs in this assay was 10 ng/mL. For additional confirmation of drug presence, the same chromatographic method was used, however, the mass spectrometry analysis was performed using semi-quantitative full MS-data dependent MS2 (i.e. tandem mass spectrometry), where the precursor ions are detected at high resolution, and upon detection of the precursor, a subsequent fragmentation event occurs and the product ions are detected and analyzed.

To minimize laboratory error, controls for each drug were analyzed at the lower limit of detection and a mid-level concentration were are run on each plate at the beginning, middle, and end of each run. If there were any significant differences between 2 sets of controls, then all specimens between those controls were re-run. In addition, there was an internal standard used in each sample as part of the processing (protein precipitation). If the internal standard did not meet criteria for acceptance, then that sample was considered invalid and re-processed and re-analyzed. Positive results were visually inspected to ensure that the peak shape was consistent with a standard chromatographic peak, and not distorted.

HIV-1 drug resistance testing was performed on sera with detectable ARV drugs and an unsuppressed HIV viral load at the Medical Research Council/Uganda Virus Research Institute laboratory (MRC/UVRI laboratory) in Uganda, a WHO accredited facility for HIV-1 genotyping and HIV drug resistance testing, as previously described [15]. Briefly, RNA was extracted using the QIAamp Viral RNA extraction Mini-kit (Qiagen, Hilden, Germany) and genotypic analysis was performed with nested polymerase chain reaction (PCR) of protease (codons 1–99) and reverse transcriptase (codons 1–242). Amplified products were then sequenced with Applied Bio-systems 3130 and 3500 genetic analyzers (Applied Biosystems, Foster City, CA) and base-called using Sequencer v5.2.4 (Gene Codes Corp, Ann Arbor, Michigan, USA). The Stanford HIV Drug Resistance Database was used to assign drug resistance mutations (DRMs). The partial viral genomes generated for this manuscript have been deposited in GenBank under the accession numbers MG576331-42.

Statistical analysis

Demographic characteristics were compared between HIV-positive persons who did or did not self-report ART use and significant differences were assessed by chi-square tests. Laboratory confirmation of ART use was defined has having ≥2 detectable ARV drugs in the serum, a criterion based on prior literature and examination of levels of viral load suppression per number of ARV drugs detected [9–13]. Sensitivity, specificity, positive predictive values, and negative predictive values were estimated for the full study population and for various demographic sub-populations using the “EpiR” package. All statistical analyses were performed using the R statistical software (version 3.2)

RESULTS

Of the 557 HIV-positive participants who were tested for ARV drugs, 153 (27%) self-reported ART use. Among those who self-reported ART use, 44% (n=68) reported receiving their ART from Ministry of Health clinics supported by Rakai Health Sciences Program and 54% (n=83) reported receiving ART from other non-governmental organizations, including Uganda Cares or and The AIDS Support Organization. Only two participants reported receiving treatment from private clinics.

Individuals who self-reported ART use were more likely to be older, female, work in agriculture, and self-report cotrimoxazole use (Table 1). In contrast, participants who resided in the high prevalence fishing community and participants who had never been married were significantly less likely to report ART use. HIV viral load suppression was 86% (n=132/153) among HIV-positive persons who self-reported ART use and 21% (n=83/404) among those who did not self-report ART use ($p<0.001$).

ARV drugs were detected in 36% (n=203/557) of participants, including 98% (n=150/153) of persons who self-reported ART use. Among those with ≥1 detectable ARV drugs, 11 (5%) had one ARV detected, 137 (67%) had two ARV drugs detected, 52 (26%) had three ARV drugs detected, and 3 (1.5%) participants had four ARV drugs detected (Supplemental Table 1). Of those who self-reported ARV use, 97% (n=148/153) had at least two ARV drugs detected. Levels of ARVs were significantly lower among those with no self-reported ARV use with only 11% (n=44/404) having two or more ARV drugs detected. Viral load testing was performed for 98% (n=548/557) of participants. Viral load suppression was similar among those with two ARV drugs detected (92%; n==123/134) and ≥3 ARV drugs detected (90%; n=47/52). Suppression was substantially lower among individuals with no or only one detected ARV drugs: 40% (n=4/10) of persons with one ARV drug were suppressed and 12% (n=41/352) with no drugs detected were suppressed. Among 83 persons with a suppressed viral load and no self-reported ART use, 51% (n=42) had one or more ARV drugs detected.

Overall, the most frequently detected ARV drugs were zidovudine (ZDV), lamivudine (3TC), nevirapine (NVP), and efavirenz (EFV) (Table 2). Among those with detectable ARVs, 182/203 (90%) had two or more ARVs detected in combinations consistent with one of two first line regimens prescribed in Uganda at the time of this study: 3TC/NVP/ZDV and 3TC/EFV/ZDV. There were 107 participants with 3TC/NVP detected, 34 with 3TC/NVP/ZDV detected, 30 with 3TC/EFV detected, and 11 participants with 3TC/EFV/ZDV detected. Four participants had at least two ARV drugs included in the available second-line ART regimen (Lopinavir [LPV] and Ritonavir [RTV] in combination with 3TC and TFV). There were 28 pregnant HIV+ women of whom 15 (53.6%) had ARV drugs detected. All but one of these latter women had at least two ARV drugs detected with the exception of one woman who only had ZDV detected and an unsuppressed HIV viral load (786 copies/ml).

Using ≥2 ARV drugs detected as laboratory confirmation of ART use, the overall sensitivity was 77% (95%CI: 70–83%) the specificity was 99% (95%CI: 97–100%) for self-reported

ART use. Using the HPLC data, prevalence of ART use in our study population was 34% (95%CI: 31–39%) which was higher than the self-reported apparent prevalence of 27% (95%CI: 24–31%). Positive and negative predictive values, which depend on the prevalence of ART use, were also high: the positive predictive value of self reported ART use was 97%(95%CI:0.93–0.99) and the negative predictive value was 89% (95%CI: 86–92%).

Sensitivity and specificity of self-reports did not differ by gender or by residence in a fishing community (Table 3). However, sensitivity increased steadily with age ($p<0.001$) from a low of 55% (95%CI: 23–83%) among adolescents 15–19 years to a high of 89% (95%CI: 78–96%) among those over forty years. Sensitivity was significantly lower among traders (57%; 95%CI: 39–74%) relative to persons in the most frequently reported occupation of agriculture ($p<0.001$). Specificity did not fall below 95% in any of sub-groups analyzed.

Drug resistance genotyping was performed for the subset of participants with ≥1 detectable ARV drugs and an unsuppressed HIV viral load. There were 22 participants who met these criteria of whom 17 had remaining sample available for genotyping. Of these 17 participants, five did not amplify by PCR on retest (four of five of these individuals initially had HIV viral loads <5000 copies/ml). Eleven of twelve participants with genotyping results and unsuppressed viral load had ≥1 drug resistant mutation all of which were NRTI resistant mutations (Supplemental Table 2). The majority (n=10/11) also had NNRTI mutations. NRTI resistance mutations included MV184 (n=11/11), T215F (n=2/11), K65R (n=1/11), K219E (n=1/11), and T215Y (n=1/11). NNRTI resistance mutations included K103N (n=5/11), Y181C (n=4/11), G190A (n=3/11), and Y188C (N=1/11). We found no resistance to protease inhibitors.

DISCUSSION

In this population-based study of HIV-positive persons in Uganda, we find that self-reported ART use has high specificity and moderate sensitivity. Overall, these data suggested that self-reported data on ART use provide reasonable but conservative estimates of population-level ART use. We find no difference in the validity of self-reported ART use by gender or between communities of varying HIV prevalence.

While few people reported using ART when no ART was detected in their blood, 23% of persons with ≥2 detectable ARV drugs in their plasma did not disclose ART use suggesting moderate levels of underreporting in this population. In two clinical trial populations in sub-Saharan Africa, prevalence of undisclosed ART use among enrollees with undetectable viral load was ~46% [9, 10] which was similar to the 51% prevalence detected in this study. We also found younger persons and individuals who were traders were less likely to disclose ART use relative to older age groups and other occupations. Barriers to accurate self-reported ART use in these sub-groups should be investigated in future studies. Of note, ART eligibility criteria has expanded since this study was conducted resulting in an increasing proportion of young HIV-positive persons being prescribed ART. Consequently, more inclusive ART eligibility guidelines may lower the overall sensitivity of self-reported data; however, it is conceivable that barriers to self-reported ART use may be mitigated by its more widespread use.

Among persons who had detectable ARV drugs and unsuppressed viral loads, most had genotypes with drug resistance mutations to both NRTIs and NNRTIs suggesting that self-reported ART use in the presence of a detectable viral load is indicative of possible non-adherence and/or treatment failure. Genotyping results were consistent with a prior study in Rakai, which detected the same drug resistance mutations at similar frequencies[15, 16]. It is important to emphasize that drug resistance testing was not performed for all HIV-positive individuals and therefore we did not evaluate population prevalence of drug resistance.

There are limitations to this study. These results may not be generalizable to populations outside of Rakai, Uganda; however, the study participants are similar to other rural Ugandan populations when compared to data from the Demographic and Health Surveys [17]. Additionally, because positive and negative predictive values depend on the underlying prevalence of ART use in the population, these values should not be extrapolated to other populations with different or unknown prevalence of ART use. Also, ART regimens typically consist of three ARV drugs; however, the majority of persons with detectable ARV drugs in this study only had two ARV drugs detected. Specifically, ZDV was only detected in 25% of participants with ≥2 ARV drugs consistent with first line ART regimens prescribed in Uganda at the time of this study. This is likely due to the pharmacokinetics of ZDV, which has a limit of detection of 20 ng/mL, and a half-life of 1–3 hours, so the drug can be cleared in 5–15 hours after a single dose. We do not have any information of when the blood sample was collected relative to when the previous dose was taken. Therefore, if the dose was taken in the morning and the specimen collected in the evening, it is possible that the drug would not be detected. In addition, if the subject were to have missed a dose or was not fully adherent, then the drug could be missed by the assay; however, 92% of individuals with 2 detectable ARV drugs had undetectable HIV viral loads which is comparable to the suppression levels among those with 3 detectable ARV drugs (90%). We also detected several unusual drug combinations in a minority of cases (e.g. 3TC/NVP/EFV, 3TC/Darunavir/LPV/NVP). This may indicate off label use of ARV drugs; however, we cannot rule out the possibility of laboratory error. Lastly, we were unable to assess the relationship between stigma and undisclosed ART, which may be a critical barrier to self-reported ART use in our study population.

In conclusion, we find that self-reported ART use has moderate sensitivity and high specificity providing conservative population-based estimates of ART use. We observe minimal over-reporting of ART use and modest levels of underreported ART use. Underreporting was more common in young persons and traders. A deeper understanding of the barriers to self-reported ART use may help improve population-based ART coverage estimates from self-reported data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institute of Mental Health (R01MH107275), the National Institute of Allergy and Infectious Diseases (1R01AI128779-01, R01AI110324, K01AI125086), and Division of Intramural

Research of the National Institute for Allergy and Infectious Diseases, the World Bank, and the Johns Hopkins University Center for AIDS Research (P30AI094189). This work was also supported (in part) by the HIV Prevention Trials Network (HPTN) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Child Health and Human Development (NICH/HD), National Institute on Drug Abuse, National Institute of Mental Health, and Office of Aids Research, of the NIH, DHHS (UM1 AI068613). We also thank the Rakai Community Cohort Study participants and study team.

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Table 1

Demographics and selected characteristics of 557 HIV-positive participants in the Rakai Community Cohort Study by status of self-reported ART use

	No self-reported ART use (N=404) N (%)	Self-reported ART use (N=153) N (%)	χ^2p-value
Gender			
Female	233 (69)	103 (31)	
Male	171 (77)	50 (23)	0.048
Age in years			
15–24	60 (90)	7 (10)	
25–29	118 (87)	17 (13)	
30–34	102 (73)	37 (27)	
35–39	66 (61)	43 (39)	
40+	58 (54)	49 (46)	<0.001
Resides in fish landing site			
No	164 (64)	91 (36)	
Yes	240 (79)	62 (21)	<0.001
Marital status			0.280
Never married	35 (81)	8 (19)	
Married, monogamous	210 (74)	73 (26)	
Married, polygamous	39 (71)	16 (29)	
Previously married	120 (68)	56 (32)	<0.001
Occupation			
Agriculture	85 (59)	58 (41)	
Fishing	68 (85)	12 (15)	
Trading	70 (76)	22 (24)	
Bar/Restaurant Work	33 (67)	16 (33)	
Other	148 (77)	45 (23)	<0.001
Self-reported cotrimoxazole use			
No	298 (95)	14 (5)	
Yes	106 (43)	139 (57)	<0.001
HIV virally suppressed (copies/ml <400) *			
No	317 (95)	16 (5)	
Yes	83 (39)	132 (61)	<0.001

* Nine individuals were missing a viral load measurement.

Table 2

ARV drug combinations detected by HPLC by gender among those with detectable ARV drugs (n=203)

	Women with detectable ARV drugs (N=138)		**Men with detectable ARV drugs (N=65)**	
	Self-reported ART use		***Self-reported ART use***	
ARV drug combinations detected by HPLC	**No N=37 (%)**	**Yes N=101 (%)**	**No N=16 (%)**	**Yes N=49 (%)**
3TC/NVP	28 (76)	50 (50)	6 (38)	23 (47)
ZDV/3TC/NVP	2 (5)	25 (25)	1 (6)	6 (12)
3TC/ EFV	1 (3)	12 (12)	5 (31)	12 (24)
ZDV/3TC/EFV	-	5 (5)	-	6 (12)
NVP	3 (8)	1 (1)	-	1 (2)
3TC/Darunavir/LPV/NVP	-	2 (2)	-	-
EFV	1 (3)	-	1 (6)	-
FTC/LPV/RTV	-	2 (2)	-	-
3TC/LPV/RTV	1 (3)	1 (1)	-	-
LPV	-	-	2 (12)	-
3TC/NVP/EFV	-	-	-	1 (2)
3TC/Abacavir//NVP	-	1 (1)	-	-
ZDV/3TC/NVP/EFV/ZDV	-	1 (1)	-	-
3TC/NVP/Tenofovir	-	1 (1)	-	-
Rilpivirine	-	-	1 (6)	-
ZDV	1 (3)	-	-	-

3TC=Lamivudine, NVP=Nevirapine; ZDV=Zidovudine; EFV=Efavirenz; FTC=Emtricitabine; RTV=Ritonavir; LPV=Lopinavir

AIDS. Author manuscript; available in PMC 2019 January 28.

Table 3

Sensitivity, specificity, and positive and negative predictive values of self-reported ART use

	≥2 ARV drugs Detected/Total (%)	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
Overall	**192/557 (34)**	**0.77 (0.70, 0.83)**	**0.99 (0.97, 1.00)**	**0.97 (0.93, 0.99)**	**0.89 (0.86, 0.92)**
Gender					
Male	60/221 (27)	0.80 (0.68, 0.89)	0.99 (0.96, 1.00)	0.96 (0.86, 1.00)	0.93 (0.88, 0.96)
Female	133/336 (39)	0.76 (0.68, 0.83)	0.99 (0.96, 1.00)	0.97 (0.92, 0.99)	0.86 (0.81, 0.90)
Age in years					
15-24	11/67 (16)	0.55 (0.23, 0.83)	0.98 (0.90, 1.00)	0.86 (0.42, 1.00)	0.92 (0.82, 0.97)
25-29	23/135 (17)	0.61 (0.39, 0.83)	0.97 (0.92, 1.00)	0.82 (0.57, 0.96)	0.92 (0.86, 0.96)
30-34	50/139 (36)	0.74 (0.60, 0.85)	1.00 (0.96, 1.00)	1.00 (0.91, 1.00)	0.87 (0.79, 0.93)
35-39	53/109 (49)	0.79 (0.66, 0.89)	0.98 (0.90, 1.00)	0.98 (0.88, 1.00)	0.83 (0.72, 0.91)
40+	55/107 (51)	0.89 (0.78, 0.96)	1.00 (0.93, 1.00)	1.00 (0.93, 1.00)	0.90 (0.79, 0.96)
Resides in fish landing site					
No	108/255 (42)	0.82 (0.74, 0.89)	0.99 (0.95, 1.00)	0.98 (0.92, 1.00)	0.88 (0.93, 0.93)
Yes	84/302 (28)	0.70 (0.59, 0.80)	0.99 (0.96, 1.00)	0.95 (0.87, 0.99)	0.90 (0.85, 0.93)
Marital status					
Never married	9/43 (21)	0.78 (0.40, 0.90)	0.97 (0.85, 1.00)	0.88 (0.47, 1.00)	0.94 (0.81, 0.99)
Married, monogamous	90/283 (32)	0.79 (0.69, 0.87)	0.99 (0.96, 1.00)	0.97 (0.90, 1.00)	0.91, (0.86, 0.94)
Married, polygamous	19/55 (35)	0.79 (0.54, 0.94)	0.97 (0.85, 1.00)	0.94 (0.70, 1.00)	0.90 (0.76, 0.97)
Previously married	74/176 (42)	0.74 (0.63, 0.84)	0.99 (0.95, 1.00)	0.98 (0.90, 1.00)	0.84 (0.76, 0.90)

	≥2 ARV drugs Detected/Total (%)	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value (95%CI)	Negative predictive value (95%CI)
Occupation					
Agriculture	62/143 (43)	0.92 (0.82, 0.97)	0.99 (0.93, 1.00)	0.98 (0.91, 1.00)	0.94 (0.87, 0.98)
Fishing	15/80 (19)	0.73 (0.45, 0.92)	0.98 (0.92, 1.00)	0.92 (0.62, 1.00)	0.94 (0.86, 0.98)
Trading	35/92 (38)	0.57 (0.39, 0.74)	0.96 (0.88, 1.00)	0.91 (0.71, 0.99)	0.79 (0.67, 0.87)
Bar/Restaurant Work	21/49 (43)	0.76 (0.53, 0.92)	1.00 (0.88, 1.00)	1.00 (0.79, 1.00)	0.85 (0.68, 0.95)
Other	59/193 (31)	0.75 (0.62, 0.85)	0.99 (0.88, 1.00)	0.98 (0.88, 1.00)	0.90 (0.84, 0.94)
Self-reported cotrimoxazole use					
No	47/312 (15)	0.30 (0.17, 0.43)	1.00 (0.99, 1.00)	1.00 (0.77, 1.00)	0.89 (0.85, 0.92)
Yes	145/245 (59)	0.92 (0.87, 0.96)	0.95 (0.89, 0.98)	0.96 (0.92, 0.99)	0.90 (0.82, 0.95)
HIV virally suppressed (copies/ml <400) *					
No	16/333 (5)	0.75 (0.48, 0.93)	0.99 (0.97, 1.00)	0.75 (0.48, 0.93)	0.99 (0.97, 1.00)
Yes	170/215 (79)	0.77 (0.70, 0.83)	0.98 (0.88, 1.00)	0.99 (0.96, 1.00)	0.53 (0.42, 0.64)

* Nine individuals were missing a viral load measurement