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Retesting of Patients Receiving Antiretroviral Treatment at HIV Care and Treatment and Prevention of Mother-To-Child HIV Transmission Sites in Cameroon

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Abstract

The World Health Organization recommends retesting of newly diagnosed HIV cases for verification of results prior to antiretroviral therapy (ART) initiation. This study aimed at ascertaining the HIV status of clients on lifelong ART. We tested 25% of ART clients in 6 care and treatment (C&T) sites and all HIV-positive women receiving ART in 22 prevention of mother-to-child HIV transmission (PMTCT) sites in Northwest and Southwest regions. Testing was proposed consecutively to clients in group education sessions during ART refill visit until the sample size was achieved. Individual counselling was provided to clients who opted to be retested. Testing was with Determine HIV-1/2 and First Response rapid tests and further testing was with DNA-PCR. Clients with negative test results were counseled to discontinue ART. Results were analyzed comparing misdiagnosis at ART and PMTCT sites. A total of 4526 ART clients were retested for HIV; 3914(86.5%) from ART and 612(13.5%) from PMTCT sites. Female participants dominated (79%) and the median age was 39 years. Higher proportions of clients retested at PMTCT sites were negative with both tests (0.8% vs 0.1%) and had discordant results (1.1% vs 0.4%) than at ART sites. All 32 clients with negative or discordant results were tested with DNA-PCR and 22(0.5%) were negative; 11(0.3%) in ART and 11(1.8%) in PMTCT sites. HIV positive status was confirmed for 99.5% of clients retested, with a lower rate at PMTCT (98.2%) than C&T (99.7%) sites; meaning misdiagnosis and inappropriate ART treatment was more likely at PMTCT. Adherence to recommendation for HIV retesting for verification will reduce inappropriate treatment.

Keywords*: HIV, Retesting, Misdiagnosis, Care and Treatment Centre, PMTCT, Cameroon.*

Introduction

Western and Central Africa is home to 4.7 million people living with HIV (PLWHIV), constituting 2% of PLWHIV globally. Of these PLWHIV, 73% were on HIV treatment by the end of 2020 with 22% of the world's HIV-related deaths occurring in this sub region [1, 2]. HIV prevalence in Cameroon is 3.7% with a total of 500,000 PLWHIV;71,4% of whom are on ART [3-5]. The Cameroon Baptist Convention Health Board (CBCHB), a faith based organization, has provided HIV care and treatment since 2002 and 23,800 PLWHIV have received treatment at CBCHB facilities and over 175,000 at CDC/PEPFAR supported sites [4, 6]. The national guidelines for HIV testing in Cameroon recommend the use of two different rapid test kits in a serial testing algorithm for persons aged 18 months and above for the

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purpose of diagnosis. In the case of blood transfusion, a parallel testing.

lgorithm using both the first and the second HIV test concomitantly is used [7]. Determine HIV-1/2 rapid test was the first test used and a second rapid test was used, if the Determine test was positive. The choice of the second rapid test depended mostly on availability, ease of use and required storage facilities. Prior to 2017, it was not a routine in Cameroon to repeat HIV test for people with documented HIV positive status before initiating ART. The WHO 2016 second edition guidelines for the use of antiretroviral drugs for treatment and prevention of HIV, recommended that clients who tested HIV positive should be placed on treatment irrespective of disease stage and the CD4 count value [8]. Cameroon adopted this guideline, and the Minster of Public Health issued a circular and held press conferences to promote its implementation [7].

HIV testing is carried out in the community and at all health facilities by trained laboratory staff, nurses, some trained paramedical staff, and community workers due to the demand creation for testing. The recommended HIV testing algorithm required two rapid tests performed successively on the same sample with positive results before the client is declared HIV positive. The implementation of this recommendation varied across sites based on the level of understanding of the new guidelines and availability of stock of HIV test kits. Information on Quality assurance (QA), Quality Control (QC) and test kits used was not well documented due to regular change of the HIV testing registers, limited knowledge and skill of staff and frequent transfer of trained staff. The lapses in QA/QC for HIV testing and the procedure for verification of the HIV status before linkage for treatment increased the risk of misdiagnosis and inappropriate ART initiation. This risk could even be higher in the context of pregnant women who were initiated early on ART without sufficient verification of their HIV status. There are several reports in the published literature and unpublished program data of HIV status misclassification, both for false positive and false negative results [9, 10]. False-positive diagnosis for HIV among client already on ART was established to range from 2.6% in Burundi to 10.5% in the Democratic Republic of Congo [11]. These reports have raised concerns that some individuals might have been put on ART inappropriately. The 2015 WHO guidelines recommended retesting of all newly diagnosed persons with a second specimen before ART initiation, to rule out potential misdiagnosis [12].

This study assessed the results of HIV retesting of clients of 22 PMTCT and 6 ART sites to validate their HIV status. Misdiagnosis for HIV is predominantly caused by serological cross reactivity, although other hypothesized programmatic and quality-related factors include:

1. Improper transport and storage of test kits,
2. User errors in conducting the test or recording the results,
3. Lack of clear standard operating procedures (SOPs) and training,
4. Improper use of the testing algorithm and lack of supportive supervision [13].
5. Poor choice of assays for the testing algorithm (low specificity of second/third assay or poor choice of assay due to cross-reactivity associated with other infections or pregnancy),
6. Non-compliance with test procedure (e.g., altered reading time, using a confirmatory assay (second- or third-line assay) as a screening assay (instead of a first line assay),
7. Incorrect amount of buffer applied to test strip, and
8. Incorrect interpretation of or recording of test results (e.g., weak positive, clerical errors) [11].

Additional testing is critical to distinguish true positive from false positive [14]. It is recommended that if there is any doubt regarding the diagnosis of HIV, the individual

should be referred to other centers for confirmatory testing and diagnosis [15].

In 2013, WHO recommended initiation of ART for all people with CD4 <500 cells/ml and based solely on HIV serological diagnosis (i.e., using RDTs or EIAs) without additional immunological (i.e., CD4 count) or virological (i.e., viral load) testing for some populations (including all pregnant women, sero-discordant couples, people with TB and severe hepatitis co-infection, and children less than 5 years of age) [16]. While emphasizing the importance and critical need of quality control in conducting HIV rapid testing and respect for testing algorithms, it is probable that a small fraction of all those currently receiving ART in C&T and PMTCT sites may not be HIV positive due to a false positive result. Therefore, all individuals whose initial HIV testing was positive, should be retested on a second blood specimen so that they will not be started on ART for life, if they are not infected with HIV. Retesting will reduce the risk of HIV status misclassification.

Methods

This study was designed, reviewed, and approved by the regional delegations of public health in the Northwest (NW) and Southwest (SW) regions of Cameroon as a public health intervention. The project lasted for four months from May through August 2016.

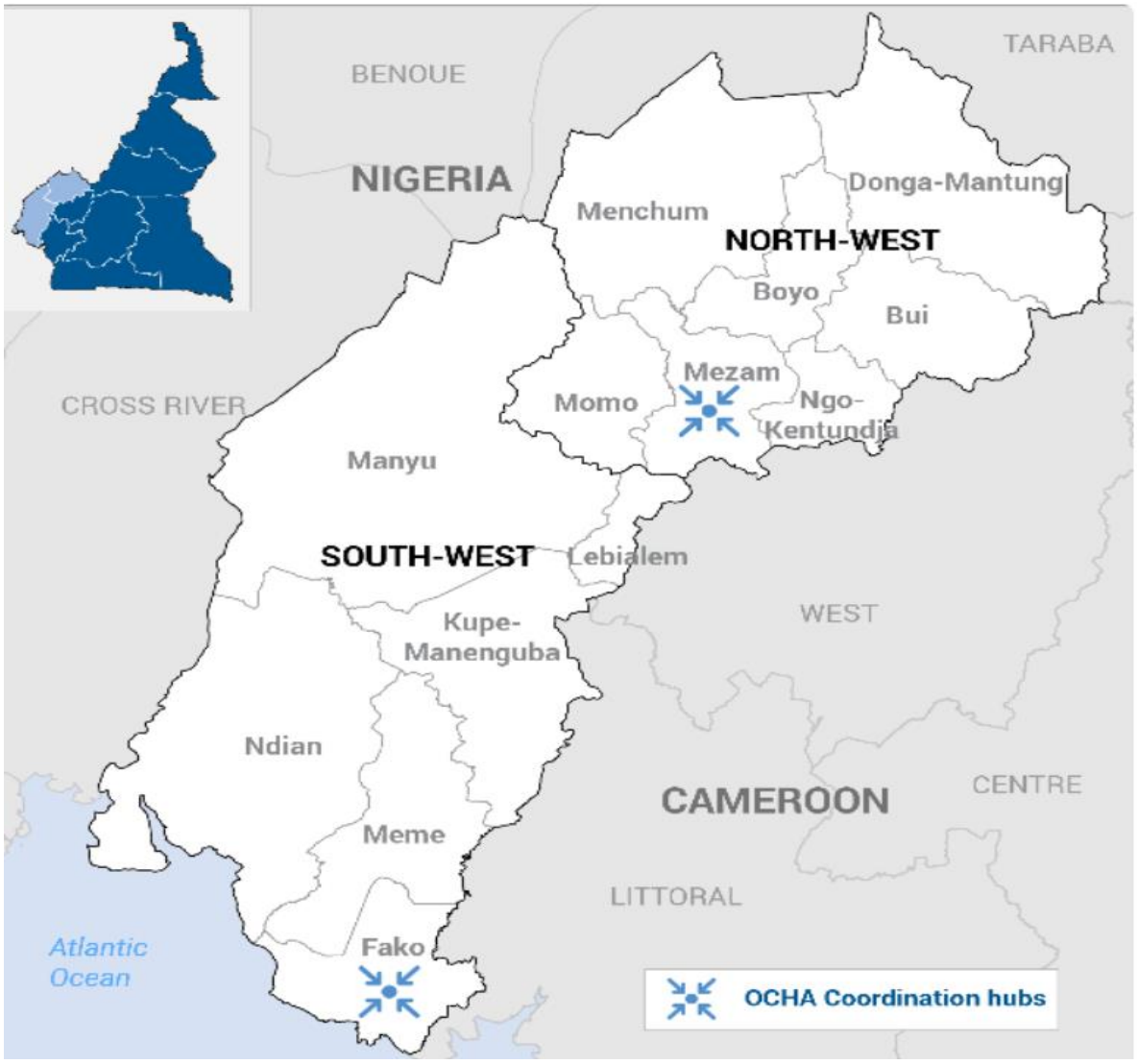

Figure 1. Map of Northwest and Southwest Regions Showing the Divisions

Assessment Site / Sample Size

A total of 28 assessment sites were purposefully selected including 22 PMTCT sites (12 in the NW and 10 in the SW) which had initiated over 600 women on PMTCT regimen following the 'test and treat' approach as a pilot and six high volume ART sites (3 in each region). The target was to retest all the women on ART in the PMTCT sites who gave consent and 25% of all the patients enrolled in the ART sites to obtain an overall sample size of 4600. A high-volume site was one with at least 2000 ART clients enrolled and included Baptist Hospital Mutenene, Buea Regional Hospital and Presbyterian General Hospital Kumba in the Southwest region and Nkwen Baptist Health Center, Bamenda Regional Hospital and Ndop District Hospital in the Northwest region. An advocacy workshop was organized for leaders of the 28 study sites involving Directors/Administrators, ART coordinators and heads of laboratories. During this meeting, information about the study was shared, the testing algorithm reviewed and all material for the study distributed. Onsite meetings were also held to educate the staff on the importance of the study and counsellors encouraged us to provide adequate information to clients. The Project Coordinator was assigned to work closely with the sites to collect weekly data, provide needed materials and support them to address concerns that came up.

Testing Process/Algorithm

Clients were informed about the assessment using a structured information sheet and they gave verbal consent before their samples were collected. The Abbott Determine HIV-1/2 and the First Response rapid test kits were used to conduct the HIV test simultaneously. If both tests were positive, the client was confirmed HIV positive. If both or either of the rapid tests was negative, a DBS sample was collected for DNA-PCR testing and sent to a reference laboratory. If the DNA-PCR test was positive, the client was confirmed HIV positive. If DNA-PCR was negative, it was repeated 3 to 6 months later before the client was confirmed HIV negative. Service providers did post-test counselling before giving the results to the clients. The clients were counselled on the need to wait for the DNA-PCR test results within 2 weeks to one month. The providers collected contact information for clients whose samples were collected for DNA-PCR test and provided follow up counselling to give their results.

Ethical Considerations

This project was a quality improvement study aimed at improving HIV testing services and reliability of HIV test results before ART initiation and used procedures that are standard of care in the context of a public health intervention and therefore, did not require an IRB oversite. An authorization was obtained from the Regional Delegations of Public Health. Group pre-test counselling was done to all the clients, and they were allowed to opt out of the retesting. The clients were told that this was a quality improvement project that will enable better care to be provided to them and for people who will need care in the future. Individual counselling was done during data collection for clients who opted to be retested, and the implications of negative results were explained. The possibility of having a negative HIV test results because of undetectable viral load due to duration on treatment and level of adherence was also explained. Also, the possibility of a negative test resulting from sensitivity/specificity of test and laboratory, or documentation error was carefully explained however, assurance was given to the clients that measures are taken to control and eliminate their occurrence. The need for further testing in the case of any discordant or negative results before conclusive results are obtained was explained to all clients.

Data Collection and Analysis

Data was collected using a pre-tested semi-structured questionnaire in all the sites which was administered by clinic staff. The data

collection was completed with charts and register review to complete missing data and to validate doubtful information. The questionnaires included both close-ended and open-ended questions. Variables of interest included date of first positive test, type of rapid test done, if test was repeated prior to starting treatment, date of treatment initiation, first and most recent CD4 counts with dates, WHO clinical staging at the time of treatment initiation and current ARV regimen. There was also a laboratory form where the retesting results were recorded with provision for the name and signature of laboratory technician. Data was entered into a database that was designed using Microsoft access and was exported and analyzed in STATA versionn14.0. Descriptive analysis was done with frequencies and percentages calculated, comparing PMTCT and ART sites.

Results

Overall HIV Retesting Results and Demographic Characteristics

A total of 16,600 clients were receiving ART at 28 (22 PMTCT and 6 C&T) sites. Of these, 4526 (27.3%) were retested for HIV and 32 (0.1%) were either negative or discordant for both serologic tests. The discordant or negative clients were all retested by DNA-PCR for confirmation. Of all clients retested, 22 (0.5%) were virologically confirmed negative. Figure 2 shows the flow of HIV retesting from all ART clients in the study sites to confirmatory results. Of the participants, 79% were females and the median age was 39 (IQR: 3-78) years, with the male being averagely older than the female. Table 1 presents the demographic characteristics of the study participants.

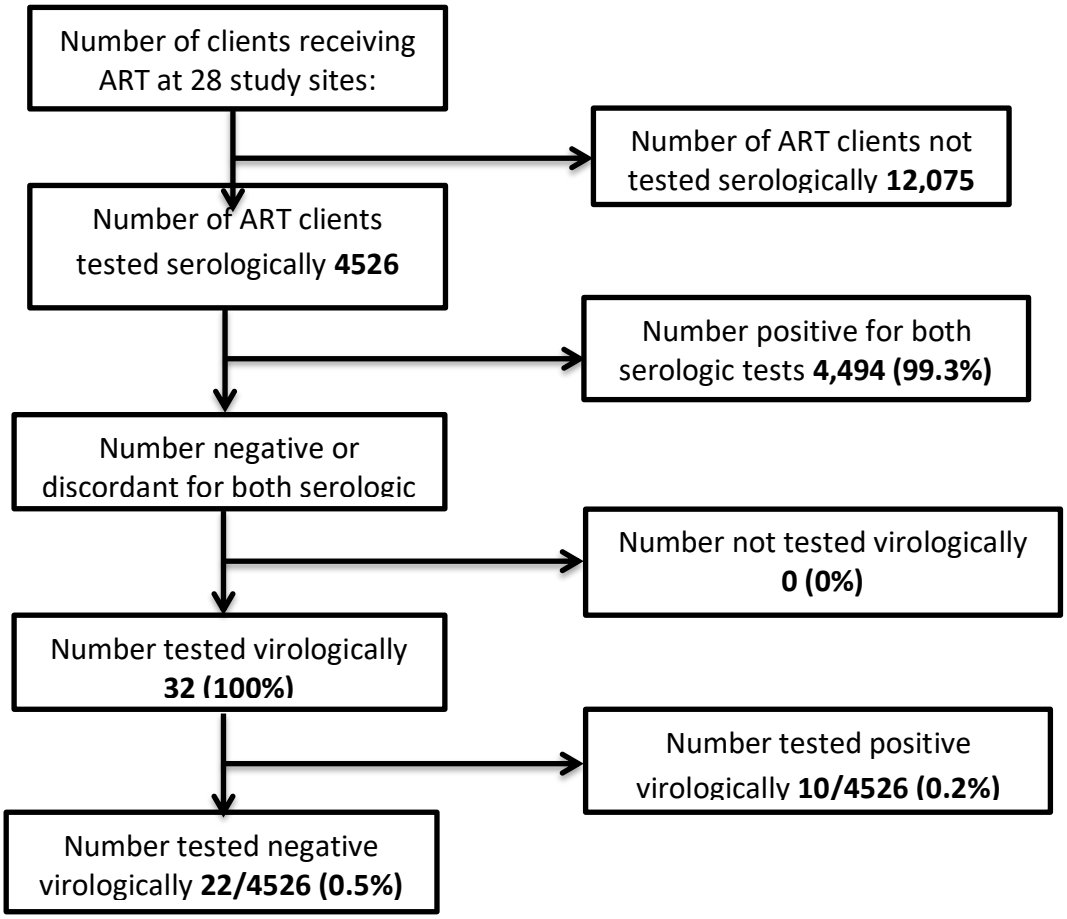

Figure 2. Flow Chart of HIV Retesting of ART Clients at 28 Study Sites (But for Number Tested Negative Virologically whose Denominator is Number of ART Client Tested Serologically, Percentages Use Denominator from the Box in the Previous Step)

Table 1. Demographic Characteristics of ART Client Retested for HIV

Variables/Level	PMTCT		**C&T**		**ALL SITES**	
	N=612	**%**	**N=3914**	**%**	**N=4526**	**%**
Sex						
Male	N/A	N/A	951	24%	951	21%
Female	612	100%	2963	76%	3575	79%
Median age (IQR), years	29 (19-45)	N/A	41 (2-78)	N/A	39 (3-78)	N/A
Age group (Years)						
<15	0	0%	43	1%	43	1%
15-24	101	17%	98	3%	199	4%
25-44	504	82%	2289	58%	2793	62%
≥ 45	7	1%	1484	38%	1491	33%

Clinical Information

35% of study participants who started ART at WHO stage 1 disease, 22% at stage II, 36% at stage III and 6% at stage IV. The majority (89%) of clients initiating ART at PMTCT sites were at WHO HIV stage I, while a greater proportion of the participants from the care and treatment sites were initiated at stage III (42%). The median time from diagnosis to ART initiation was 3.3 years. Most (71%) of the study participants were initiated on Tenofovir Lamivudine Effavirenz (TELE) while 17% were on trimune and the remaining 12% on other regimens. The participants had been on treatment for a median duration of 4.4 years. Table 2 presents the details of the clinical information of the study participants.

Table 2. Clinical Information of ART Clients Retested for HIV

Variables/Level	**PMTCT**		**C&T**		**ALL SITES**	
	N=612	**%**	**N=3914**	**%**	**N=4526**	**%**
WHO staging at the start of treatment						
Stage I	544	89%	1057	27%	1601	35%
Stage II	51	8%	960	25%	1012	22%
Stage III	15	2%	1634	42%	1649	36%
Stage IV	2	0%	263	7%	265	6%
Median time (IQR) to initiation, years	1.3 (0.7-1.6)	N/A	3.9(1.9-6.)	N/A	3.3(1.4-5.8)	N/A
Treatment regimen at time of retesting						
TELE	570	93%	2622	67%	3192	71%
Trimune	10	2%	771	20%	781	17%
Others	32	5%	521	13%	553	12%
Median duration (years) of clients on ART drugs						
All ART clients	2.0 (0.3-15)	N/A	5.1 (0.3-26)	N/A	4.4 (0.3-26)	N/A
Clients positive by DNA-PCR	1.1 (0.5-1.9)	N/A	3.6 (0.7-8.5)	N/A	1.7 (0.5-8.5)	N/A
Clients negative by DNA-PCR	-	N/A	2.2 (0.7-7.8)	N/A	2.2 (0.7-7.8)	N/A

Documentation of Initial Rapid Test and Retesting Results

Of the initial HIV tests done, documentation was available for 55% of participants who had two or more tests and 10% who had only one test. However, the results from 35% of the participants tested was missing, largely because some clients were not tested at the study sites. The initial HIV rapid tests were done using Determine for 49% of the tests, First Response for 35%, Bioline for 13% and others, including Oraquick and Acon for 3% of the tests. Of the ART clients who were serologically retested for HIV verification, 11 were negative for both tests and 21 were discordant. Higher proportions of clients retested in PMTCT clinics were negative with both tests (0.8% versus 0.1%) and had discordant results (1.1% versus 0.4%) than in ART sites. Among the 32 clients who were either negative or discordant by serologic test who were tested by DNA-PCR, 10 were positive while 22 were negative. A significantly (P<0.01) higher proportion of clients who were both negative or discordant by serology and negative by DNA-PCR were in the PMTCT sites than the C&T sites (1.8% versus 0,3%). The median duration of participants on ART prior to the study was 4.4 (IQR: 0,3-26) years. Table 3 presents the details of documentation of initial HIV tests and the results.

Table 3. Documentation of HIV Rapid Test and Retesting Information

Variables/Level	PMTCT		C&T		ALL SITES	
	N=612	%	N=3914	%	N=4526	%
Number of Participants with Documented Information on Initial HIV Tests Done						
≥ Two Tests	385	63%	2111	54%	2496	55%
One Test	72	12%	400	10%	472	10%
None	155	25%	1403	36%	1558	35%
Type of Rapid Test Kit Used for Initial HIV Tests						
Determine	448	48%	2455	49%	2903	49%
First Response	330	35%	1715	34%	2045	35%
Bioline	82	9%	675	14%	757	13%
Others	82	8%	142	3%	221	3%
Number of tests kits used	939	100%	4997	100%	5926	100%
HIV serologic retesting results						
Positive for both serologic tests	600	98.0%	3894	99.5%	4494	99.3%
Negative for both serologic tests	5	0.8%	6	0.1%	11	0.2%
Discordant by serologic tests	7	1.1%	14	0.4%	21	0.5%
HIV confirmatory test by DNA-PCR						
Number of DNA-PCR tests done	12	100.0%	20	100.0%	32	100.0%
Number positive by DNA-PCR	1	0.2%	9	0.2%	10	0.2%
Number negative by DNA-PCR	11	1.8%	11	0.3%	22	0.5%

Discussion

The study participants were predominantly females and their median age was 39 years (IQR:3-68) which are consistent with findings of other Cameroon studies that established median age of ART clients at 39.3 and 39.7 years[1]. We found that most (89%) of the PMTCT participants started on ART at WHO stage I, while majority (42%) of those of the Care and Treatment sites started WHO stage III. The high female proportion of the study participants is influenced by the female from PMTCT sites. This finding aligns with the May 2013

guidelines that stressed the importance of early ART treatment for pregnant women for their own health and to prevent HIV infection in their infant [17]. Consistent with this, the median time from HIV diagnosis to ART initiation was significantly lower at 1.3 years for PMTCT clients compared with 3.9 years for clients of Care and Treatment.

The 10% of the study participants who had documented information only for one test and the absence of documented information of the initial test for 35% of the participants suggests either non-adherence to testing algorithm and poor documentation, which are key quality issues likely to have contributed to misdiagnosis.

This project found that 0.5% of patients in PMTCT and C&T sites were inappropriately diagnosed as HIV positive and started on ART which is similar to the 0.4% and 0.6% misdiagnosis that has been reported in studies conducted in South Africa and Swaziland [18]. The risk of inappropriately placing people on ART was significantly higher at 1.3% among ART clients at PMTCT sites compared with 0.3% in clients at care and treatment sites. This is much lower than the 4.5% (43/952) pre-ART VL results of <50 copies/ml established in a study in South Africa but higher than the 0.3% that obtained after confirmation with ELISA in the same study. The 0.3% confirmed negative by DNA-PCR test at C&T sites was same as the results after confirmation with ELISA in the South African study[19]. The primary benefit of this project was that individuals who were found to be HIV negative were able to stop ART. Health providers should consistently retest HIV positive clients prior to initiation of ART.

Conclusion

Results from this quality improvement project confirmed that 99.5% of clients on life-long ART (99.7% at care and treatment sites and 98.2% at PMTCT sites) in the Northwest region of Cameroon are HIV positive. The study helped to identify 22(0.5%) individuals who were inappropriately receiving ART and properly counseled them to discontinue the treatment.

Complete adherence to current HIV testing recommendations is critical for mitigating inappropriate diagnosis and inappropriate. Additionally, consisted use of recommended rapid test kits which are properly stored, and careful documentation will further minimize chances of inappropriate diagnosis and its associated discomforts. This will minimize the chances of some people having psychological trauma and profound social effects; marital issues and taking HIV treatment which they do not need [20].

Competing Interests

The authors hereby declare that they have no conflicts of interest.

Acknowledgement

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