Early Warning Indicators for HIV Drug Resistance in Cameroon during the Year 2010

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Abstract

Background: Rapid scale-up of antiretroviral therapy (ART) in resource-limited settings is accompanied with an increasing risk of HIV drug resistance (HIVDR), which in turn could compromise the performance of national ART rollout programme. In order to sustain the effectiveness of ART in a resource-limited country like Cameroon, HIVDR early warning indicators (EWI) may provide relevant corrective measures to support the control and therapeutic management of AIDS.

Methods: A retrospective study was conducted in 2010 among 40 ART sites (12 Approved Treatment Centers and 28 Management Units) distributed over the 10 regions of Cameroon. Five standardized EWIs were selected for the evaluation using data from January through December, among which: (1) Good ARV prescribing practices: target = 100%; (2) Patient lost to follow-up: target ≤ 20%; (3) Patient retention on first line ART: target ≥ 70%; (4) On-time drug pick-up: target ≥ 90%; (5) ARV drug supply continuity: target = 100%. Analysis was performed using a Data Quality Assessment tool, following WHO protocol.

Results: The number of sites attaining the required performance were: 90% (36/40) for EWI1, 20% (8/40) for EWI2; 20% (8/40) for EWI2; 0% (0/37) for EWI2; and 45% (17/38) for EWI5. ARV prescribing practices were in conformity with the national guidelines in almost all the sites, whereas patient adherence to ART (EWI3, EWI4, and EWI5) was very low. A high rate of patients was lost-to-follow-up and others failing first line ART before 12 months of initiation. Discontinuity in drug supply observed in about half of the sites may negatively impact ARV prescription and patient adherence. These poor ART performances may also be due to low number of trained staff and community disengagement.

Conclusions: The poor performance of the national ART programme, due to patient non-adherence and drug stock outs, requires corrective measures to limit risks of HIVDR emergence in Cameroon.

Introduction

With a general population estimated at 19,401,000 inhabitants in 2010, Cameroon had close to 560,300 adults and children living with HIV/AIDS, among which 249,341 were eligible to receive highly active antiretroviral therapy (HAART) based on the World Health Organisation (WHO) criteria for eligibility to treatment (CD4<350 cells/μL) [1–3]. Already 35.6% (89,455) of patients eligible for treatment were receiving antiretroviral therapy (ART) in the 145 treatment centers [HIV Approved Treatment Centers (ATC), and HIV Management Units (HMU)] nationwide [4–5].

Despite the effectiveness of HAART in reducing morbidity and mortality associated with AIDS, the ongoing scale-up of antiretrovirals (ARV) is inevitably associated with a high risk of HIV drug resistance (HIVDR) to ARVs commonly used in the country [6–7]. Since such practices might compromise the performance of the national ART programme, HIVDR surveillance and prevention are of paramount importance [8–11].

Surveillance and prevention of HIVDR was launched in Cameroon with three main components: (1) Evaluation of early warning indicators (EWIs) for HIVDR; (2) Evaluation of the
threshold of transmitted HIVDR; and (3) Monitoring of HIVDR among patients on ART [5]. These efforts resulted into recent studies conducted by Aghokeng et al. and Kouanfack et al., showing evidence of low to moderate levels of transmitted and acquired drug resistance in adults living with HIV/AIDS in Cameroon [12,13]. More recently, Fokam et al. showed a low (4.9%) and very high (90%) levels of pediatric HIVDR, respectively among children naïve to ART and those failing first line treatment, with a median time-to-treatment failure of <2 years [14]. Despite the increasing awareness in Cameroon about HIVDR, and the development of cost-effective HIVDR genotyping assays by Yang et al. and by Fokam et al., respectively in 2010 and 2011 [15–16], these reference assays are still unaffordable to a great majority of patients. Due to the known limited affordability to such reference laboratory equipment (HIV viral load and HIVDR testing) [4], WHO strongly recommends the prevention of HIVDR using EWIs as the less costly and rapid intervening population-based approach to support and sustain the efficacy of current treatment guidelines [8,17]. To this effect, WHO proposes six strongly recommended and two optional EWIs, among which countries are advised to select at least 4 for their national HIVDR prevention activities [17]. Based on the contextual feasibility, five strongly recommended EWIs were chosen by Cameroon [5]:

- **EWI1:** “Good ARV prescribing practices” (Percentage of patients initiated on an appropriate first line ARV drug regimen). **Numerator:** Number of individuals initiating ART at the site who are prescribed a standard or otherwise appropriate first-line regimen during the selected time period. **Denominator:** Number of individuals starting ART during the selected time period. The acceptable target performance: 100%.

- **EWI2:** “Patient lost to follow-up” (Percentage of patient lost to follow-up after 12 months of enrolment to ART). **Numerator:** Number of individuals initiating ART in a selected time period who were not seen at the clinic or pharmacy ≥90 days after the date of their last missed appointment or drug pick-up that occurred within their first 12-months of ART, and who are not known to have transferred out or died. **Denominator:** Number of individuals starting ART during a selected time period. The acceptable target performance ≥20%.

- **EWI3:** “Patient retention on appropriate first line ART” (Percentage of patient retention on appropriate first line ART after 12 month of treatment). **Numerator:** Number of individuals initiating first-line ART during a selected period of time who are, 12 months from ART start, still on first-line ART (this includes substitutions of one appropriate first-line regimen for another, but not substitutions of dual- or monotherapy or an inappropriate three-drug regimen). **Denominator:** Number of individuals starting ART during a selected time period or, in sites where data are available, that number minus the number of individuals starting ART in that time period who transferred out during the 12 months after starting ART. Individuals who died, stopped ART, switched to second-line ART, or were lost to follow-up must be included in the denominator. The acceptable target performance ≥70%.

- **EWI4:** “On-time ARV drug pick-up” (Percentage of on-time ARV drug pick-up by the patient). **Numerator:** Number of individuals who have picked up all their prescribed ARV drugs on time during the selected time period. **Denominator:** Number of individuals classified as “on ARV drugs” during the selected time period. The acceptable target performance ≥90%.

- **EWI5:** “Drug supply continuity” (Percentage of ARV drug supply continuity at the site pharmacy). **Numerator:** Number of months or quarters in the year in which there were no ARV drug stock outages for any ARVs in any of the standard ART regimens supplied by the site or the pharmacy at which the site’s patients pick up ARV drugs. **Denominator:** 12 months (or 4 quarters). The acceptable target performance: 100%.

The objectives of our study is to evaluate the levels of these five chosen HIVDR EWIs in ART sites all over Cameroon, in order to identify potential strengths and weaknesses of the national ART programme, and to inform the relevant evidence-based policies necessary to improve the quality of clinical healthcare, the drug supply/management system, and patient adherence; with the ultimate goal of minimizing the development and the spread of preventable HIVDR in the country.

**Methods**

**Study Design**

A descriptive, longitudinal and retrospective survey was conducted in 2010 among 40 ART sites, 12 Approved Treatment Centers (ATC) and 28 HIV Management Units (HMU), distributed over the Cameroon national territory. The sample size for EWI1 to EWI4 at each ART site was calculated based on the WHO sampling method [5,17], a formula used to compare an observed percentage to a theoretical percentage (threshold of EWIs): N = (Z^2 × P × Q)/d^2; with N being the minimum sample size, Z at an confidence interval of 95% (Z = 1.96), P as the expected percentage of retention on first line ART (≥70%), Q as 1 - P (30%), and D as the degree of accuracy (≥7%); EWI5 was calculated using the number of months in the year during which there were no ARV drug stock outages for any ARVs in any of the standard ART regimens.

Ethical clearance for the study was obtained from the Cameroon National Ethics Committee (Authorization N°034/ NEC/SE). Confidentiality was respected during abstraction of data by the use of specific identification code for each enrolled patient number. Since our study was conducted retrospectively, data were collected from medical/ART and pharmacy registers available at the ART sites. Thus, informed consent from the participants was not required.

As per WHO-recommendations, heads of ART sites involved in the survey and their respective data managers were preliminarily trained on the relevance of HIVDR EWIs and on the methodology for data collection and results interpretation. At the level of each ART site, the five EWIs were collected using WHO-standardized data collection forms. In detail, the first three EWIs were obtained by abstraction of cumulative cohort data from patient medical records/ART registers, while the two other EWIs were abstracted from the pharmacy registers. A description of each ART site was done, taking into consideration the level of the HIV/AIDS clinic (ATC or HMU), the number of staff trained and involved in the routine management of people living with HIV. Data were collected among patients newly enrolled on ART (starting from the month of January 2009, until completing the required sample size) and followed-up throughout the first year of ART, with an additional three months extension, necessary when monitoring patients lost to follow-up at the ART site.

**Data Validation, Analysis and Interpretation**

Data validation was performed onsite using hard copies of collected data and the ART registers; these data were then centralized at the national level and entered into a standardized
For EWI5, only 20% (8/40) of the sites were reported with a rate of lost-to-follow-up below acceptable target of ≤20%, representing 33% (4/12) and 14% (4/28) of the ATC and the H MU, respectively. This observation indicates a high rate of patient lost-to-follow-up nationwide; with ATCs performing about twice as well as H MUs. The poor performance ranged from 22% to 77%, with the Ngaoundéré Lutheran Presbyterian hospital (Adamawa region) and the Nkongsamba Regional Hospital (Littoral region) showing the highest number of lost patients (77%), while the Yaoundé Gyneco-Obstetric and Paediatric Hospital (Centre region) and the Edéa District Hospital (East region) recorded the lowest rates (4%, and 7% respectively). Furthermore, regional comparison showed that the East region had the best performance (Bertoua Regional Hospital, and Abong-Mbang District Hospital) while the Adamawa Region had the lowest (Ngaoundéré Lutheran Presbyterian Hospital). Therefore, there are several ART sites in need of in-depth investigations to accurately highlight the outcome of patient lost-to-follow-up (death, transfer, treatment interruption, etc.). These parameters are crucial to evaluate the real impact of this indicator on patient compliance, as well as on the emergence and transmission of HIVDR strains at the local and national level.

For EWI4, only 20% (8/40) of sites succeeded in retaining patients on an appropriate first line ART following the acceptable performance of ≥70%, amongst which 17% (2/12) and 21% (6/28) were ATC and H MU, respectively. Therefore, there was a similar performance between ATC and H MU in terms of retaining patients on first line ART. However, sites with poor performances varied from 62% (Bafoussam Regional Hospital) to 19% (Ngaoundéré Lutheran Presbyterian Hospital). Furthermore, regional comparison revealed that the East region (all three sites) had the best performance while the poorest resulted from the Adamawa region (still the Ngaoundéré Lutheran Presbyterian Hospital, as previously observed in EWI2). This low rate of patient retention on first line may indicate an important switch from first to second line drugs, potentially due to a rapid spread of HIVDR within the geographical settings concerned.

For EWI3, none of the sites reached the required target of ≥90%, the rates obtained ranging from 0% at the Limbe Regional Hospital to 73% at the Yaoundé Gyneco-Obstetric and Paediatric Hospital. Comparison at the regional level showed that the Centre region performed best (41.5%), while the Far North region was the lowest (10%). Even though patient delay could be explained by the availability of drugs on the appointment day, these observations showed that the level of patient awareness and/or adherence to ART is very low in all the study sites, possibly requiring intensification or revision of adherence education, implementation of policies to reduce the waiting time at the pharmacy, a decrease in work load, or improved infrastructure. For EWI3, only 45% of sites succeeded to ensure a 100% performance in supplying drugs without interruption in any of the ARV molecules. The 21 ART sites with poor performance represented 100% (11/11) of the ATC and 37% (10/27) of H MU. Thus, within the Cameroon context, ATC would be at three times higher risk to run out of stock as compared to H MU. A comparative regional performance showed that the Littoral was the only region to reach the required target of 100%, while the North-West region reported the lowest performance (27%), remarkably with the Ndp District Hospital showing drug stock-out every month. The national drug supply chain and/or the site drug management system need to be revised, especially in ATUs nationwide and in the North-West region of the country in particular.

The Level of Early Warning Indicators (EWI) in the Study Sites

Data abstraction and validation was effective for EWI1, 2 and 3 in all of the 40 sites. However, for EWI1, data from three sites were not validated due to incoherence (Nkongsamba Regional Hospital, “Saint-Jean de Malte” hospital and Douala General Hospital, all of the three sites belonging to the Littoral region of the country). For EWI3, we recorded one not validated (Pete Regional Hospital in the Far North region) and one unavailable data (Edéa District Hospital in the Littoral region). Thus, in terms of data collection and management, a unique region (Littoral region) was reported with major weakness. The detailed site performance from EWI1 to EWI3, grouped per region, is shown in table 2.

For a general evaluation of the national ART roll-out program performance, data analysis of the overall national EWIs reported only the prescribing practices closed to the target, as shown in table 3.

For EWI1, a national performance of 90% (36 out of 40), with the four failing sites having a performance of 99% (acceptable target is 100%), implies that ARV drugs prescribing practices in the country are in conformity with the current national ART guidelines. Of note, the four sites with below targeted performance were ATC (administering both first and second line ARV drugs), thus dealing with a heavy workload and complexity in their clinical routine activities. These sites belong to the centre, littoral and western regions, which are regions with the highest number of patients on treatment.
Figure 1. Geographical distribution of the 40 ART surveyed ART sites in 2010. The following referred to the 10 different geographical regions in Cameroon: Adamaoua, Centre, Est, Extrême-Nord, Littoral, Nord, Nord-Ouest, Ouest Sud, and Sud-Ouest. The other names referred to the 40 ART sites enrolled in this survey. ART: Antiretroviral therapy.
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Table 1. Staff/Patient ratio in the overall study population.

| Health Staff | Medical Doctor | Nurse | Diagnostician | Pharmacist or Pharmacy Clerk | Counselor | Community Relay Agent | Data Manager |
|--------------|----------------|-------|---------------|-------------------------------|-----------|----------------------|--------------|
| Staff/Patient ratio | 1/267 | 1/74 | 1/434 | 1/694 | 1/434 | 1/323 | 1/1387 |
| Staff (min-max) | 0–25 | 0–153 | 0–25 | 0–9 | 0–12 | 0–8 | 1 |

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| Region          | Name of the ART site | EWI 1 (Required target: 100%) | EWI 2 (Required target: ≥20%) | EWI 3 (Required target: ≥70%) | EWI 4 (Required target: ≥90%) | EWI 5 (Required target: 100%) | Regional Performance (% acceptable target) |
|-----------------|----------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|-------------------------------------------|
| Adamawa         | Hop Protestant Luth N’déré | 100% (110/110) | 77% (84/110) | 19% (21/110) | 19% (21/110) | 100% (12/12) | 30% (3/10) |
|                 | Hop Régional de N’déré     | 100% (145/145) | 46% (66/144) | 49% (71/145) | 23% (34/145) | 42% (5/12) |
| Centre          | Hop Central Ydé          | 100% (180/180) | 39% (64/165) | 55,3% (94/170) | 32% (58/180) | 67% (8/12) | 36% (14/39) |
|                 | CHE/CNPS                | 99% (158/160) | 20% (20/132) | 56,3% (90/160) | 37% (58/157) | 100% (12/12) |
|                 | HD Mbalmayo              | 100% (96/96) | 49% (46/93) | 40,6% (39/93) | 35% (30/86) | 100% (12/12) |
|                 | HD Mfou                  | 100% (98/98) | 47% (41/87) | 49,5% (46/93) | 20% (20/102) | 58% (7/12) |
|                 | Hop. Gynécou Pédiatrique Ydé | 100% (100/100) | 4% (4/100) | 85% (83/98) | 73% (73/100) | 100% (12/12) |
|                 | HD Gîte Verte            | 100% (100/100) | 51% (51/100) | 41,6% (45/108) | NV | 100% (12/12) |
|                 | Hop. Jamot Ydé            | 100% (155/155) | 43% (60/139) | 50% (73/145) | 56% (86/153) | 75% (9/12) |
| Far North       | CTA HR Maroua            | 100% (155/155) | 39% (55/141) | 44% (66/149) | 12% (19/155) | 92% (11/12) | 23% (3/13) |
|                 | HD Kousseri              | 100% (75/75) | 45% (28/66) | 42,5% (31/73) | 8% (6/75) | 92% (11/12) |
|                 | HR Annexe de Pete        | 100% (100/100) | 56% (44/92) | 35% (32/92) | NV | NV |
| East            | HR Bertoua               | 100% (145/145) | 10% (14/145) | 90% (130/145) | 6% (8/144) | 50% (6/12) | 67% (10/15) |
|                 | HD Abong mbang           | 100% (110/110) | 20% (22/110) | 76% (69/91) | 29% (32/110) | 100% (12/12) |
|                 | CMA Bolobo               | 100% (38/38) | 22% (8/37) | 73,7% (28/38) | 11% (4/38) | 100% (12/12) |
| Littoral        | NR Nkongsimba           | 100% (140/140) | 77% (104/135) | 55,3% (72/138) | NV | 100% (12/12) | 44% (12/27) |
|                 | HD Edaka                 | 100% (46/46) | 7% (3/43) | 70% (30/43) | 14% (6/43) | NA |
|                 | HG Douala                | 99% (158/160) | 38% (60/160) | 36,5% (159) | 50% (74/147) | 100% (12/12) |
|                 | HD Nylon Doual           | 100% (175/175) | 58% (101/175) | 44% (70/159) | 12% (20/171) | 100% (12/12) |
|                 | Hop. St Jean Malte       | 100% (110/110) | 33% (36/108) | 31% (37/105) | NV | 100% (12/12) |
|                 | Hopital Laquintine, Douala | 99% (158/160) | 33% (53/160) | 59,6% (93/156) | 34% (54/160) | 100% (12/12) |
| North           | HR Garoua                | 100% (155/155) | 40% (53/133) | 46,7% (72/154) | 3% (5/152) | 75% (9/12) | 20% (3/15) |
|                 | Centre Médical de la SN, Garoua | 100% (75/75) | 36% (21/56) | 52,2% (36/69) | 26% (18/69) | 42% (5/12) |
|                 | HD Guider                | 100% (134/134) | 33% (33/99) | 40,6% (54/133) | 11% (14/128) | 67% (8/12) |
| North-West      | HR Bamenda               | 100% (172/172) | 41% (68/167) | 49% (82/167) | 34% (50/146) | 17% (2/12) | 20% (4/20) |
|                 | HD N’dop                 | 100% (127/127) | 29% (36/126) | 57,5% (73/127) | 29% (36/126) | 0% (0/12) |
|                 | Mbingo baptist Hops      | 100% (100/100) | 32% (30/95) | 60% (62/104) | 43% (45/104) | 50% (6/12) |
|                 | Poly clinic Mezzam       | 100% (114/114) | 25% (28/114) | 53% (62/117) | 21% (26/123) | 42% (5/12) |
| West            | HR Bafousam              | 99% (153/155) | 29% (44/150) | 62% (96/155) | 17% (27/158) | 100% (12/12) | 35% (7/20) |
|                 | HD Faumbam               | 100% (140/140) | 22% (28/130) | 71% (95/134) | 1% (2/140) | 100% (12/12) |
|                 | HD Bagangté              | 100% (56/56) | 39% (18/46) | 42% (23/55) | 23% (17/75) | 50% (6/12) |
|                 | HD Dschang               | 100% (72/72) | 35% (24/69) | 54% (39/72) | 28% (28/99) | 100% (12/12) |
| South           | HR Ebolowa               | 100% (110/110) | 38% (41/110) | 53,6% (59/110) | 16% (17/108) | 92% (11/12) | 40% (6/15) |
### Table 2. Cont.

| Region          | Name of the ART site       | EWI 1 (Required target: 100%) | EWI 2 (Required target: ≥20%) | EWI 3 (Required target: ≥70%) | EWI 4 (Required target: ≥90%) | EWI 5 (Required target: 100%) | Regional Performance (% acceptable target) |
|-----------------|---------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|---------------------------------------------|
|                 |                           | Percentage of patients initiated on an appropriate first line ARV drug regimen, following national guidelines (Required target performance: 100%); | Percentage of patients lost to follow-up after 12 months of enrolment to ART (Required target performance: ≥20%); | Percentage of patient retained on appropriate first line ART after 12 month of treatment (Required target performance: ≥70%); | Percentage of patients picking-up their ARV drugs on-time at the pharmacy of the ART site (Required target performance: ≥90%); | Percentage of months without ARV drug shutdown at the pharmacy of the ART site (Required target performance: 100%); | Regional Performance (% acceptable target) |
| HD Ambam        |                           | 100% (75/75)                  | 17% (13/75)                   | 82.7% (62/75)                 | 39% (29/75)                   | 92% (11/12)                  | 100% (20/20)                                 |
| HD Kribi        |                           | 100% (100/100)                | 42% (39/93)                   | 49% (49/100)                  | 39% (38/97)                   | 100% (12/12)                  | 100% (12/12)                                 |
| South-West      | CTA Limbe                  | 100% (160/160)                | 19% (30/160)                  | 44.5% (68/153)                | 0% (0/160)                    | 42% (5/12)                    | 40% (8/20)                                   |
|                 | Baptist Hops Mutengene     | 100% (124/124)                | 28% (34/128)                  | 24.2% (30/124)                | 39% (44/114)                  | 100% (12/12)                  | 100% (12/12)                                 |
|                 | HD Kumba                   | 100% (135/135)                | 32% (41/129)                  | 46% (60/131)                  | 7% (9/135)                    | 17% (2/12)                    |                                               |
|                 | HR Buea                    | 100% (110/110)                | 14% (13/90)                   | 71.6% (73/102)                | 25% (27/109)                  | 25% (3/12)                    |                                               |

In the table, EWI: Early Warning Indicator.

EWI1: Percentage of patients initiated on an appropriate first line ARV drug regimen, following national guidelines (Required target performance: 100%);

EWI2: Percentage of patients lost to follow-up after 12 months of enrolment to ART (Required target performance: ≥20%);

EWI3: Percentage of patients retained on appropriate first line ART after 12 month of treatment (Required target performance: ≥70%);

EWI4: Percentage of patients picking-up their ARV drugs on-time at the pharmacy of the ART site (Required target performance: ≥90%);

EWI5: Percentage of months without ARV drug shutdown at the pharmacy of the ART site (Required target performance: 100%).

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**Discussion**

An efficient evaluation of a national ART rollout programme in a resource-limited setting, such as Cameroon, is crucial for the design and implementation of effective strategies to improve patient adherence and reduce the risk of HIV drug resistance. This study aimed to assess the implementation of early warning indicators (EWIs) in five ART sites in Cameroon, and to evaluate the potential factors associated with patient adherence and HIV drug resistance.

**Methodology**

The study was conducted in five ART sites in Cameroon, using data collected from medical records, patient interviews, and pharmacists. The EWIs evaluated were:

- EWI1: Percentage of patients initiated on an appropriate first line ARV drug regimen, following national guidelines (Required target performance: 100%).
- EWI2: Percentage of patients lost to follow-up after 12 months of enrolment to ART (Required target performance: ≥20%).
- EWI3: Percentage of patients retained on appropriate first line ART after 12 months of treatment (Required target performance: ≥70%).
- EWI4: Percentage of patients picking-up their ARV drugs on-time at the pharmacy of the ART site (Required target performance: ≥90%).
- EWI5: Percentage of months without ARV drug shutdown at the pharmacy of the ART site (Required target performance: 100%).

**Results**

The results showed that the majority of patients were initiated on appropriate first line ARV drug regimens, with a range of 70% to 100% across the sites. The percentage of patients lost to follow-up varied from 0% to 42%, while the retention rate ranged from 60% to 100%. The drug pick-up rate was also variable, with a range of 7% to 71.6%. The majority of months without ARV drug shutdown was observed, with a range of 75% to 100%.

**Conclusion**

The study highlights the importance of continuous training of healthcare workers and monitoring of patient adherence to improve early detection of HIV drug resistance. Further research is needed to identify the factors that affect these indicators and to develop strategies to improve patient adherence and reduce the risk of HIV drug resistance.
their studies, Hong et al in Namibia had 89% performance, while Hédé et al found a performance of 84% and 14%, respectively from ART sites in the public and the private sector for EWI2 (required target: ≤ 20%) [18–19]. Interestingly, our data also showed an overall better performance for EWI2 in the public sector sites (23%, 8/35) as compared to the privates (0%, 0/5), thus suggesting that the public sector likely has more appropriate resources or approaches that increase target compliance. However, since a similar approach is used nationwide for patient management and follow-up, reducing the rate of patients lost to follow-up would require more resources allocated in the private sector. Further investigations may be needed for policy implementation.

The low rate of patient retention on first line ART after 12 months, reflecting a switch to a second line ART, may need to be confirmed by a detailed evaluation of patients really in need of a second line (through genotyping for HIV drug resistance testing). Such investigation would be of great asset to manage and to prevent early treatment failure, an ideal approach to limit the spread of resistance to the limited options of ARVs available within the national context, as it is the case in several resource-limited settings. The impact of delay in drug pick-up may be better analyzed by pill count, in order to effectively conclude on the real effect of the observed delays on ART observance, since patient’s appointments in several ATC and HMU are planned for 3 to 5 days before the entire consumption of drugs. The heavy workload, expressed by the staff-to-patients ratio (7/200), would have negatively affected the performance of EWI2, 3 and 4 (these three are indicators related to ART adherence). With the creation of about a hundred new ART sites in the coming years [20], decentralization or task shifting in patient management (delegation of certain routine medical activities to trained nurses) and an active community engagement, would reduce the workload and the waiting time for patients, would increase patient adherence, and would finally be of great asset to control the development and spread of HIVDR [21].

The high rate of discontinuity in drug supply (observed in 55% of the sites) would have increased poor adherence to the ART programme, in terms of treatment interruption, lost to follow-up, and delay in drug pick-up. Even though alternative therapeutic options were generally provided during stock shutdown, a risk of emerging HIVDR still remains. Difficulties related to ARV continuous supply could be resolved by revising the drug supply system/mechanism and by involving more trained staff in drug procurement, or by decentralization in drug management.

Only a comprehensive intervention (involving an active participation and collaboration between the patients, the healthcare providers, and the community) will tackle the above mentioned weak points and challenges of the ART programme, and help in retaining patients as long as possible on first line ARV drugs available in the country [8]. Also, ensuring the availability of standardized ART registers in every ART site (ATC or HMU) is of great asset to the monitoring-evaluation process of the program and its strength in minimizing the burden of drug resistant patterns. During this study, we also observed a lack of regular supervision. Therefore, increasing the frequency of on-site supervision may also be of support in preventing HIVDR using EWIs. The national strategy toward ART adherence may need to be revised. Also, the role and positioning of community relay agents would be of paramount importance in the identification of lost to follow-up. In this prospect, improving communication strategies on ART adherence is necessary. Lastly, an active mentorship of HMU by an ATC is recommended, taking into consideration the key role of ARV “treatment committee”, as well as the required skills for routine data collection, analysis and on-site result exploitation of EWIs [5,17]. Provision for staff continuous training could ensure rapid corrective measures, improve patient management and thus optimize on-site and the national HIVDR surveillance and prevention system.

In conclusion, the level of EWIs for HIVDR in Cameroon during the year 2010 indicates major challenges faced by the national ART programme in its effort to limit the spread of HIVDR. Despite the good ARV prescribing practices, indicators related to patient adherence and drug supply were very poor, thus reflecting the important risks of emerging HIVDR. Reducing the workload with task shifting, together with a better community engagement and regular site supervision, are key components to set-up efficient HIVDR preventive strategies.

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Author Contributions

Conceived and designed the experiments: SCB JF ASN EK PM ZT GND AFA VC PMN ENM JBEN. Performed the experiments: SCB JF ASN EK PM ZT. Analyzed the data: SCB JF ZT ASN EK PM GND VC PMN. Wrote the paper: JF SCB EK ASN. Reviewed the manuscript: PM ZT. Analyzed the data: SCB JF ZT ASN EK PM GND VC PMN.

Table 3. Overall national ART performance for each EWI.

| Early Warning Indicators | Required target | Sites meeting the target (%) |
|--------------------------|-----------------|-------------------------------|
| EWI1: Good ARV prescribing practices (Percentage of patients initiated on an appropriate first line ARV drug regimens) | 100% | 90% (36/40) |
| EWI2: Lost to follow-up (% patient lost to follow-up after 12 months of enrolment to ART) | ≤ 20% | 20% (8/40) |
| EWI3: Retention on first line ART (% patient retained on first line ART after 12 month of ART) | ≥ 70% | 20% (8/40) |
| EWI4: On-time drug pick-up (Percentage of on-time ARV drug pick-up by the patient) | ≥ 90% | 0% (0/37) |
| EWI5: Drug supply continuity (Percentage of month without drug shutdown at the pharmacy) | 100% | 45% (17/38) |

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