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HIV-1 drug resistance in treatment-naïve, chronically infected patients in Jamaica

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Introduction

In 2010, Jamaica had an estimated prevalence of 1.7% in the general population [1]. HIV-1 subtype B has been identified as predominant [2, 3], being evident in up to 93% of cases [3]. In 2004, a public access treatment programme was established [4]. This was augmented in 2007 by the rapid expansion of antiretroviral therapy (ART) access [5]. The provision of ART follows a public health approach with standardized treatment guidelines. The ART backbones include non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz and nevirapine, and ritonavir boosted protease inhibitors (PIs), lopinavir and atazanavir.

One survey of 37 cases in Jamaica identified HIV drug resistance in 29% of treatment naïve patients [6]. In developed countries, reports have indicated an increasing prevalence of transmitted drug resistance (TDR) [7, 8]. One paper summarizing the temporal changes in TDR reported the United States as having the highest TDR prevalence at 12.9%, followed by Europe at 10.9% [7]. In developing countries, TDR prevalence was reported as 2.4% in south/southeast Asia and 3.2% in sub-Saharan Africa [9]. In Latin America reports range from 3.3% in Peru to 7.0% in Honduras [10].

The purpose of this study was to investigate the prevalence of transmitted resistance among persons with established HIV-1 infection at The Comprehensive Health Centre, the largest government sponsored HIV treatment site located in Kingston, Jamaica. The total HIV-1 population at this site was estimated to be 3,000 patients. A post-hoc analysis of applying the WHO/PAHO protocols for HIVDR surveillance is also presented.

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Methodology

A cross-sectional study of antiretroviral naïve patients and patients exposed to short-term therapy for prevention of mother-to-child transmission (pMTCT) was conducted. HIV-1 diagnosis was made based on a screening rapid HIV-1/2 antibody test and confirmed with western blot testing. Patients included in the study were 18 years of age or older, had documented HIV-1 infection and were able to provide written consent. All HIV-1 treatment naïve patients presenting consecutively at the treatment site were approached for recruitment into the study. Study accrual was completed over a 4 month period between January and April 2011.

Quantitative data was garnered via a structured data collection questionnaire and a review of patient files. Whole blood samples were collected in EDTA tubes from each participant. Processing included centrifugation and storage of the resulting plasma at -80 degrees Celsius on the same day of collection. The samples were subsequently shipped on dry ice to Ponce University in Puerto Rico where viral load assessments, sequencing of the reverse transcriptase and protease regions of the HIV-1 *pol* gene were performed, using the World Health Organization (WHO) HIV ResNet[®] protocol. Additionally, phenotypic analysis was performed utilising the VIRCO[®] virtual phenotype method. Resistance mutations were interpreted using the Stanford HIV Database algorithm [11] and the WHO HIVDR surveillance mutations (SDRM) [12].

The calculation of the sample size of 100 participants was powered ($\alpha = 0.05$) at a 95% confidence level to detect a transmitted resistance rate of 5%. All data was analysed using SPSS version 17.0 statistical software for Windows (SPSS, Chicago, IL, USA). Frequencies were used to describe categorical variables. Means with 95% confidence intervals were used to describe clinical and demographic data that are distributed normally and medians with inter-quartile ranges for those that were not. Comparisons were analysed using Chi-squared and Students t-tests with a significance level of less than 0.05.

Ethical approval for this study was provided by the University of the West Indies, Faculty of Medicine Ethics Board, Mona, Jamaica. All participants provided informed written consent prior to inclusion in the study.

Results

In this study, 103 treatment naïve HIV-1 infected participants were identified, 64 female and 39 male. The mean age at the time of the study was 37.3 years (95% C.I. 35.0 - 39.5), while the mean age at HIV-1 diagnosis was 34.5 years (95% C.I. 32.3 - 36.7) and ranged from 15 to 66 years (Table 1). The median time since HIV-1 diagnosis was 13.5 months (Inter Quartile Range 2.0 – 52.0) with 23/103 (22.3%) participants being diagnosed in the same month as study enrolment. HIV acquisition through sexual contact was reported by 98/103 (95.1%) participants, among whom 96/98 (98.0%) reported heterosexual contact and 2/98 (2.0%) male homosexual contact. The median time from last sexual exposure was reported at 12 days (IQR 4 - 31) with 56/73 (76.7%) reporting condom use during this exposure (Table 1).

There was previous exposure to ART in 8 (7.7%) of cases, all of which were associated with pMTCT. The specific regime utilized in these cases was AZT/3TC and LPV/r in 4 (57.1%) cases, AZT/3TC and NVP in 2 (28.6%) cases and 1 case of emergency prophylaxis with AZT and single dose NVP at delivery.

From the 103 samples collected there were 79 (76.6%) samples amplifiable and subsequently sequenced. Of these, 20 cases were characterized by the Stanford database as containing HIV-1 drug associated drug resistance mutations to the NRTI, NNRTI and PI classes. However, 10 cases were identified as clinically significant and were confined to the NRTI and NNRTI drug classes.

The prevalence of HIV-1 drug associated mutations known to be clinically significant was 10/79 or 12.6% (95% C.I. 5.3 – 19.9). One case exposed to pMTCT, given as emergency single dose nevirapine at delivery, had a significant mutation; the Y181C/Y mutation (Table 2). There were no cases of multiple mutations. The risk of further transmission of drug resistant viruses was identified with 9/10 cases having viral loads greater than 10,000 copies/ml (Table 2) and 7/10 cases being sexually active in the last 6 months.

The prevalence rates of TDR varied considerably between 8.0% and 25.0% with the application of the proposed WHO/PAHO inclusion criteria (Table 3). Examining cases with no known previous ART exposure and WHO SDRM reveals a TDR prevalence of 9.7% (95% C.I. 2.9 – 16.5), defined as a moderate level by the WHO.

Discussion

This study identified a prevalence of 12.6% (95% C.I. 5.3 – 19.9) of clinically significant mutations in treatment naïve individuals. These mutations were associated with resistance to the NRTI and NNRTI drug classes and comprised 20% and 80% respectively of the clinically significant mutations.

The specific HIVDR mutations identified in this study are in keeping with other studies on TDR in the region [13].

While this study was not designed using the suggested WHO protocols, the effect of applying these criteria has been clearly shown to alter the interpretation of TDR prevalence rates. Using this study methodology, including chronically infected participants, the prevalence rates of TDR are already revealing a moderate level of resistance. The inclusion of participants with earlier infection will only increase these rates. In fact, Gupta *et al* [14], were unable to show a significant difference in the prevalence of one or more HIVDR mutations between chronic and recent HIV infections in resource-limited settings.

The WHO surveillance mutations exclude the V75I and the K101Q on the basis of their frequency as polymorphisms in subtype D [15] and B [11] respectively. However, the V75I mutation, in combination with the Q151M complex, causes high level resistance to all NRTIs [16] while the K101Q has been identified to have a clinically significant impact on NNRTI activity [17].

The clinical implications of HIVDR identified in this study are related to the efficacy of standard first line regimes in achieving virologic suppression [18]. National treatment guidelines from the majority of resource constrained settings, including Jamaica, follow the WHO recommendations where first line regimes are typically NNRTI-based. Several studies have identified a reduced response to first line ART in cases with TDR [9]. In addition, TDR has also been associated with delayed virologic suppression and reduced time to virologic failure [14] resulting in higher risk of HIV-1 transmission.

Several factors identified in this study create an environment favourable to the transmission of HIVDR. Approximately 75% of participants reported sexual activity within the last six months and 23% reportedly did not use condoms. In addition, those cases in which significant mutations were identified had high viral loads, above 10,000 copies, and hence an increased risk of transmission [19].

In addressing the issue of decreased efficacy of NNRTI-based first line regimes due to TDR, countries will be required to increasingly rely on more expensive PIs and newer ART agents. The need for HIVDR surveillance monitoring, along with the associated planning involved in establishing a HIVDR testing programme and the possibility of requiring resistance testing prior to ART initiation, will add significant cost to national HIV programmes.

This study highlights the need for improvements in the quality of care for PLHIV including a greater focus on prevention techniques, such as adherence to ART and safe sexual practices. The strengthening of these HIV treatment components has the potential to limit both the development of TDR and the onward transmission of HIVDR [20].

Conclusion

HIVDR in the treatment naïve population is emerging in Jamaica. Unless addressed, HIVDR can significantly increase the costs of ART provision while simultaneously reducing the effectiveness of currently available first line ART, jeopardising the potential of Treatment as Prevention, and ultimately, undermining the response to the HIV epidemic.

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Table 1
Demographics, Clinical Characteristics and Risk Behaviour

Mean Age (n=103)	37.3 (95% C.I. 35.0 - 39.5)
Stage of Presentation (n=80)	
- Asymptomatic	50 (62.5%)
- Minor symptoms	16 (20.0%)
- Advanced HIV	9 (11.3%)
- AIDS	5 (6.3%)
Reported mode of transmission (n=98)	
- Heterosexual	96 (94.2%)
- Homosexual	2 (2.0%)
Last reported sexual exposure <6 months (n=103)	
- Yes	75 (72.8%)
- No	28 (27.2%)
Condom use at last sexual exposure (n=73)	
- Yes	56(76.7%)
- No	17 (23.3%)
CD4 Counts cells/mm³ (n=65)	
- <200	4 (6.1%)
- 200-350	8 (12.3%)
- 350-500	16 (24.6%)
- >500	37 (56.9%)
Viral load copies/ml (n=103)	
- <1,000	13 (12.6%)
- 1,000-3,000	25 (24.3%)
- >3,000	65 (63.1%)

Table 2
Characteristics of Cases with Clinically Significant Mutations

Study Number	Year of Diagnosis	Age at Diagnosis	Previous ART Exposure	Mutation	CD4 Cell Count	Viral Load	WHO Category	HIV-1 Subtype
8	2009	33	Nil	V75I/V	635	23,150	1	B
18	2010	47	Nil	K103K/N	424	15,400	1	B
75	2008	29	Nil	K103N	420	25,100	2	B
79	2010	30	sd NVP ^a	Y181C/Y	-	127,000	-	B and D
124	2008	39	Nil	T215S	448	27,700	1	B
128	2010	65	Nil	K103K/N	324	46,400	3	B
132	2010	52	Nil	K103K/N	-	112,000	3	B
140	2010	22	Nil	K103N	604	3,995	1	B
170	2009	29	Nil	K101Q	89	328,000	4	B
221	2010	22	Nil	K103N	157	36,000	4	B

^a sd NVP: Single dose nevirapine at delivery

Table 3
Application of WHO/PAHO Criteria for HIVDR Threshold Surveys

WHO Criteria	TDR Prevalence Rate
Ageless than 25 years	2/12 (16.6%)
WHO CategoryHigher than stage III or IV	4/50 (8.0%)
CD4 Cell CountGreater than500 cells/mm ³	2/26 (7.6%)
WHO Surveillance Mutation	8/79 (10.1%)
No Known Previous ART Exposure	9/72 (12.5%)
All	1/4 (25.0%)