Pharmaco-Virological Outcome and Resistance Profiles among Togolese Adolescents Transitioning to DTG

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Rodion Y. Konu [1,2], Elom O. Takassi[3], Gilles Peytavin[4], Nina Dapam[5], Florence Damond[6], Adam W. Oumarou[2], Meryem Zaidi[6], Anna-Maria Franco-Yusti[6], Quentin Le Hingrat[6], Romain Coppée[6], Claver A. Dagnra[7], Diane Descamps[6], Didier K. Ekouevi[2,8,9] and **Charlotte Charpentier[6]**

1 Département de Santé Publique, Université de Lomé, Faculté des Sciences de la Santé, Lomé, Togo; 2 Centre Africain de Recherche en Epidémiologie et en Santé Publique (CARESP), Lomé, Togo ; 3 Service de pédiatrie, CHU Sylvanus Olympio, Université de Lomé, Lomé, Togo; 4 Service de Pharmacologie, Université Paris Cité, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France; 5 Espoir Vie Togo, Lomé, Togo; 6 Service de virologie, Université Paris Cité, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, Paris, France; 7 Laboratory of Molecular Biology and Immunology, University of Lomé, Lomé, Togo; 8 Faculty of Health Sciences, Department of Public Health, University of Lomé, Center for Training and Research in Public Health, Lomé, Togo; 9 Research Institute for Sustainable Development (IRD), University of Bordeaux, INSERM, Bordeaux Population Health Centre, UMR 1219, Bordeaux, France.

E-mail contact: charlotte.charpentier@aphp.fr

BACKGROUND

- Since the latest new WHO recommendations, most countries have switched to Tenofovir-Lamivudine-Dolutegravir (TLD) regimen in the last years
- Very few data are available on the efficacy of transitioning to TLD in pediatric and young populations in West Africa
- The aim of this study was to evaluate PK-virological outcomes and genotypic resistance profiles in case of virological failure in ARV-treated children and adolescents Togolese

METHODS

- A cross-sectional study was conducted among 3 clinical centers in Lomé, capital of Togo, following children and adolescents living with HIV
- Plasma VL was determined using COBAS®/COBAS 6800® HIV-1 Test, v2.0 (Roche, Branchburg, NJ, USA)
- Plasma ARV drugs concentrations were measured by Ultra Performance Liquid Chromatography combined with tandem mass spectrometry
- Next-generation sequencing (NGS) of protease, RT and integrase regions was performed using Oxford-Nanopore Technologies (threshold fixed at 10%)
- Drug resistance mutations (DRM) were identified and resistance interpretation was performed using ANRS|MIE algorithm (hivfrenchresistance.org)

RESULTS

Patients' characteristics

- 264 subjects were enrolled with a median age of 17 years (IQR = 13-19); and 127 (48%) were men
- 85.6% were receiving a DTG-based regimen (n = 226) and 9.1% a NNRTI-based regimen (n = 24)
- Median duration since initiation of the first-line regimen was 8 years (IQR = 5-12)
- Median duration of DTG-based regimen was 20.5 months (IQR = 12.8-24.7)

PK-virological outcome

- The virological suppression was achieved in 61%, 75%, and 82% of participants at the HIV VL threshold of 50, 200 and 1 000 c/mL, respectively
- **Among the 226 subjects receiving a DTG-based regimen, 66% had VL <50 c/mL, 80% <200 c/mL and 88% <1 000 c/mL**

In this cross-sectional study of 226 Togolese children and adolescents receiving TLD since 20 months in median, 80% had VL <200 c/mL and INSTI DRM were detected in 9.4% of failure.
This advocates the need to monitor DTG drug resistance, to mitigate the risk of resistance acquisition and subsequent possible transmission.

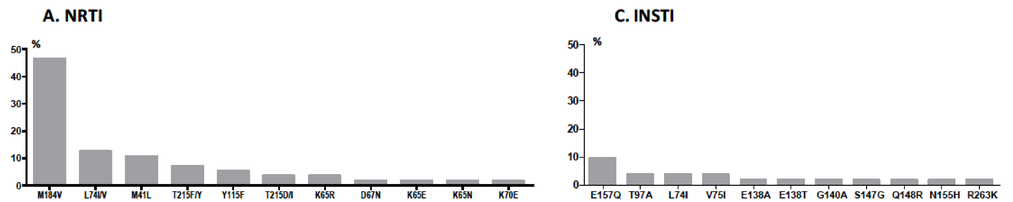

Figure 2. Prevalence of drug resistance mutations for NRTI, NNRTI, integrase strand transfer inhibitors (INSTI), and protease inhibitors

RESULTS

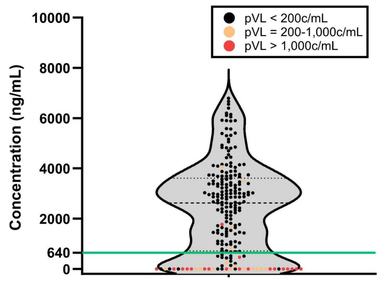

Figure 1. Description of dolutegravir (n = 224) concentrations according to plasma HIV viral load

- DTG plasma concentrations were (Fig 1): adequate (*i.e.* >640 ng/mL) in 73.8%, suboptimal in 7.4%, and <LOQ in 18.8% of the participants
- The proportions of participants with VL <200 c/mL were 32.6% (n = 14/43), 60.0% (n = 9/15) and 94.0% (n = 156/166) when plasma DTG concentrations were <LOQ, suboptimal, and adequate, respectively

Genotypic resistance tests (Figures 2 & 3)

- Overall, NGS was performed for the 66 samples with VL >200 c/mL and successful for 92%, 85%, and 76% of the samples for protease, RT and integrase, respectively
- The most prevalent subtype was CRF02_AG (n = 43, 65%)
- At least one NRTI and/or NNRTI DRM was detected in 81% of the samples (n = 42)
- An INSTI major mutation was observed in 3 of the 32 (9.4%) available integrase sequences among ALWH receiving a DTG-based regimen with the following DRM: R263K, E138A-G140A-Q148R, and N155H
- Regarding these 3 patients, two were receiving TDF/3TC/DTG, and the third one was receiving ABC/3TC/DTG as first-line regimen. Plasma DTG concentrations were adequate in two and suboptimal (114 ng/mL) in the remaining one. In addition, one of these three subjects had a virus also harboring a NRTI DRM (M184V)

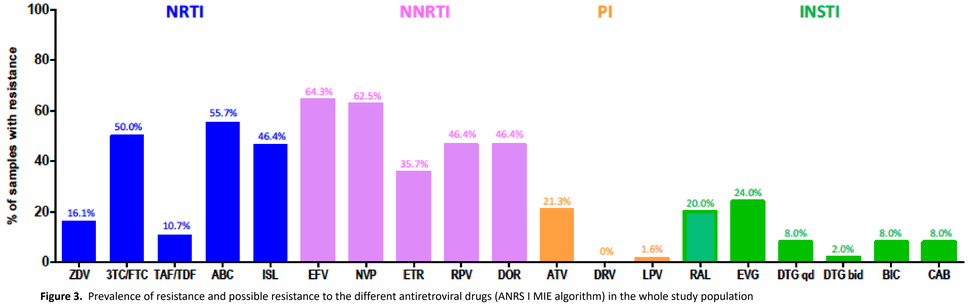

Figure 3. Prevalence of resistance and possible resistance to the different antiretroviral drugs (ANRS I MIE algorithm) in the whole study population

CONCLUSIONS

- In this cross-sectional study of Togolese children and adolescents living with HIV and receiving a DTG-based therapy, we observed a high level of virological suppression of 80% at the 200 c/mL threshold
- These first findings in such a large series of children and adolescents in low-income country, showed an INSTI DRM in 9.4% of virological failures
- Thus, even though our results confirm that use of 2nd generation INSTI is efficient for most individuals, it also advocates the need to monitor HIV drug resistance to DTG in the context of transition to TLD, with the aim of mitigating the risk of resistance acquisition and subsequent possible transmission of DTG resistance