Differences in Resistance Mutations in Non-B subtypes in First-line Failure in Africa

Kityo C, Walker S, Nankya I, Hoppe A, Thompson J, Bertagnolio S, Easterbrook P, Mugyenyi P, Paton N, EARNEST Trial Team

Earnest.cineca.org

Poster 595

Contact: earnest.mrcctu@ucl.ac.uk

Abstract (updated)

Background: Resistance mutations may vary by viral subtype, although data are limited, for non-B subtypes. Understanding the common mutational patterns is important for determining the optimal standardised regimens for the public health approach to ART provision in settings without resistance testing.

Methods: Genotypes were obtained from stored baseline samples from 792 patients aged ≥12 years who met WHO treatment failure criteria after >12 months on NNRTI-based first-line ART in the EARNEST trial in 4 sub-Saharan African countries. Subtype and drug susceptibility were determined by REGA and Stanford algorithms respectively. Presence of specific mutations and intermediate-high level resistance were modelled using multivariable logistic regression including subtype, ART exposure at first-line failure, ART prior to the failing regimen, years on first-line ART, WHO 4 events, CD4 and VL at failure.

Results: Patients had advanced treatment failure (42% VL≥100,000 c/ml, 63% CD4<100 cells/mm3). Viral subtypes were A1 (40%; Uganda, Kenya), C (31%; Zimbabwe, Malawi) and D (25%; Uganda, Kenya) with 4% recombinants/unclassified. One or more major NRTI or NNRTI mutations were found in 774 (98%); mutations to both classes were present in 747 (94%). In adjusted analyses, 4 NRTI and 7 NNRTI mutations differed significantly across the three subtypes (p<0.05; Table 1); most of these 11 mutations were significantly more common in subtype C than in A and/or D. Intermediate/high level TDF resistance (seen in 57%) was independent of subtype (adjusted p=0.38). Intermediate/high level ZDV resistance (in 71% overall) was marginally more common in subtype C (83% (adjusted)) than D (72%, p=0.05) and A (73%, p=0.06). Intermediate/high level resistance to ETR or RPV (in 51% and 62% respectively) was more common in subtype C (adjusted 63% and 76% respectively) than D (51% and 59% respectively, p<0.02) and A (47% and 60% respectively, p<001). Just 46% patients would be switched to a regimen with predicted ≥1 active NRTI using the WHO second-line treatment algorithm, but genotyping would identify a more active regimen in only an additional 35 (4%).

Conclusion: We found differences between subtypes in resistance mutations at first-line failure. The impact on residual NRTI drug susceptibility was modest. However, subtype C developed higher rates of ETR and RPV resistance, limiting their potential utility in salvage regimens in resource-limited settings.

Background

Studies comparing subtypes in patients failing first-line have to date been small (<200 patients) and thus had limited power to detect subtype differences. Subtype differences in mutational patterns might allow more refined predictions for second line ART with a public health approach .

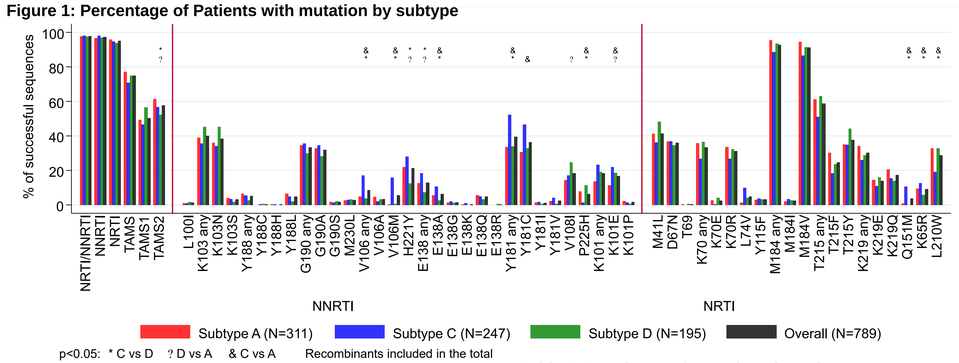
Methods

The EARNEST trial was an open-label, randomised trial performed in 14 centres in sub-Saharan Africa where HIV-positive adults and adolescents >12 years with first-line failure according to WHO modified clinical or immunological (confirmed by VL), or virological criteria were randomised to lopinavir/ritonavir 400mg/100mg twice daily with either (i) 2-3 new or recycled NRTIs ("PI/NRTI"); (ii) raltegravir 400mg twice daily ("PI/RAL"); or (iii) raltegravir induction for the first 12 weeks only ("PImono").

806 baseline samples were assayed for resistance testing. Presence/absence of individual mutations was modelled using multivariable logistic regression including subtype and ART exposure at failure, adjusting for ART exposure prior to the failure regimen, years on first-line ART, CD4 and $\log_{10}$ VL at failure, and clinical failure. Similar models were fitted to Stanford intermediate/high resistance to key drugs also adjusted for gender and age. The WHO algorithm based on treatment history was assessed against resistance testing for selecting second line NRTIs

Results

Figure 1: Percentage of Patients with mutation by subtype



Results- Mutations

Sequences were obtained in 98% of samples tested. Participants had advanced treatment failure (42% VL≥100,000 copies/ml, 63% CD4<100 cells/mm^3).

94% had both NRTI and NNRTI mutations. Only 17 (2%) patients had no NRTI or NNRTI major mutations (assumed non-adherent, median VL 116,256 c/ml vs 73,103 c/ml in those with mutations, p=0.03).

In adjusted analyses, 4 NRTI and 7 NNRTI mutations differed significantly across the three subtypes (p<0.05; Table 1 Fig. 1); most of these were significantly more common in subtype C than in A and/or D

Table 1 Prevalence of mutations by subtype

Mutation	Subtype A	Subtype C	Subtype D	Overall P	Pattern
Q151M	1%	11%	0%	<0.001, *¶	C > (A & D)
K65R	9%	13%	6%	0.002, *¶	C > (A & D)
TAM 2	61%	57%	53%	0.01, ¶†	(A & C) > D
L210W	33%	19%	33%	0.04, *¶	(A &D) > C
V106M	0%	16%	1%	<0.001, *¶	C > (A & D)
E138A	5%	10%	3%	0.004, *¶	C > (A & D)
H221Y	22%	28%	12%	0.003, ¶†	(C & A) > D
K101E	11%	22%	19%	0.02, *†	(C & D) > A
Y181C	31%	47%	33%	0.03, *	C > A
V108I	14%	17%	25%	0.01, †	D > A
P225H	8%	1%	11%	0.01, *¶	(A & D) > C

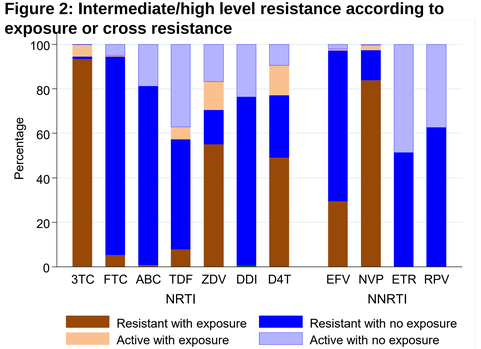
*P < 0.05 for C vs A; ¶P < 0.05 for C vs D; †P < 0.05 for D vs A

Results- Stanford Scores

Resistance and cross-resistance were common (Fig. 2). Resistance testing would identify a more active NRTI regimen in only an additional 4% compared to using the WHO algorithm.

Results- Stanford Scores (cont)

Figure 2: Intermediate/high level resistance according to exposure or cross resistance



In adjusted analysis resistance to Abacavir, Etravirine, and Rilpivirine were more common in subtype C than A or D (p<0.04) but there was no evidence of an association between subtype and Tenofovir or Zidovudine resistance.

CONCLUSIONS

Prevalence of several NRTI and NNRTI-associated mutations differed significantly across HIV subtypes, mostly being more common in subtype C vs. A and D. Higher rates of Etravirine, and Rilpivirine resistance in those with subtype C may limit their utility in second and third line regimens in resource-limited settings.

Acknowledgements

We would like to thank all the patients and staff at the EARNEST sites: JCRC Kampala: E Agweng, P Awio, G Bakeinyaga, C Isabirye, U Kabuga, S Kasuswa, M Katuramu, C Kityo, F Kiweewa, H Kyomugisha, E Lutalo, P Mugyenyi, D Mulima, H Musana, G Musitwa, V Musiime, M Ndigendawan, H Namata, J Nkalubo, P Ocitti Labejja, P Okello, P Olal, G Pimundu, P Segonga, F Ssali, Z Tamale, D Tumukunde, W Namala, R Byaruhanga, J Kayiwa, J Tukamushaba. IDI, Kampala: G Bihabwa, E Buluma, P Easterbrook, A Elbireer, A Kambugu, D Kamya, M Katwere, R Kiggundu, C Komujuni, E Laker, E Lubwama, I Mambule, J Matovu, A Nakajubi, J Nakku, R Nalumenya, L Namuyimbwa, F Semitala, B Wandera, J Wanyama. JCRC, Masaka: M Mugerwa, A Lugemwa, E Ninsiima, T Ssenkindu, S Mwebe, L Awine, H William, C Katemba, S Atunyang, M Acaku, P Ssebutinde, H Ktizo, J Kukundakwe, M Nalugoza, K Ssegawa, Namayanja, F Nsibuka, P Tuhirirwe, M Fortunate. JCRC Fort Portal: J Acen, J Achidri, A Amone, M. Chamai, J Ditai, M Kemigisa, M Kiconco, C Matama, D Mbanza, F Nambaziira, M Owor Odoi, A Rweyora, G. Tumwebaze. San Raphael of St Francis Hospital, Nsambya: H Kalanzi, J Katabaazi , A Kiyingi, M Mbidde, M. Mugenyi, R Mwebaze, P Okong, I Senoga. JCRC Mbale: M Atwola, D Baliruno, J Bwomezi, A Kasede, M Mudoola, R Namisi, F Ssennono, S Tuhirwe. JCRC Gulu (43): G Abongomera, G Amone, J Abach, I Aciro, B Arach, P Kidega, J Omongin, E Ocung, W Odong, A Philliam; JCRC Kabale: H Alima, B Ahimbisibwe, E Atuhaire, F Atukunda, G Bekusike, A Bulegyeya, D. Kahatano, S Kamukama, J Kyoshabire, A Nassali, A Mbonye, T M Naturinda, Ndukukire, A Nshabohurira, H. Ntawiha, A Rogers, M Tibyasa; JCRC Kakira: S. Kiiryа, D. Atwongeire, A. Nankya, C. Oraleku, D. Nakiboneka, D. Odoch, L. Lakidi, R. Ruganda, R. Abiriga, M. Mulindwa, F. Balmoi, S. Kafuma, E. Moriku; Zimbabwe University of Zimbabwe Clinical Research Centre, Harare: J Hakim, A Reid, E Chidziva, G Musoro, C Warambwa, G Tinago, S Mutsai, M; Phiri, S Mudzingwa, T Bafana, V Masore, C Moyo, R Nhema, S Chitongo; Malawi College of Medicine, University of Malawi, Blantyre: R Heyderman, L Kabanga, S Kaunda, A Kudzala, L Lifa, J Mallewa, M Moore, C Mtali, G Musowa, G Mwimaniwa, R Sikwese, J van Oosterhout, M Ziwoya ; Mzuzu Central Hospital, Mzuzu: H Chimbaka. B Chitete, S Kamanga, T Kayinga E Makwakwa, R Mbiya, M Mlenga, T Mphande, C Mtika, G Mushani, O Ndhlovu, M Ngonga, I Nkhana, R Nyirenda; Kenya Moi Teaching and Referral Hospital: P Cheruiyot, C Kwobah, W Lokitala Ekiru, M Mokaya, A Mudogo, A Nzioka, A Siika, M Tanui, S Wachira, K Wools-Kaloustian; Zambia University Teaching Hospital: P Alipalli, E Chikatula, J Kipala, I Kunda, S Lakhi, J Malama, W Mufwambi, L Mulenga, P Mwaba, E Mwamba, A Mweemba, M Namfukwe; The Aids Support Organisation (TASO), Uganda: E Kerukadho, B Ngwatu, J Birungi. **MRC Clinical Trials Unit**: N Paton, J Boles, A Burke, L Castle, S Ghuman, L Kendall, A Hoppe, S Tebbs, M Thomason, J Thompson, S Walker, J Whittle, H Wilkes, N Young; **Monitors**: C Kapuya, F Kyomuhendo, D Kyakundi, N Mkandawire, S Mulambo, S Senyonjo; Clinical Expert Review Committee: B Angus, A Arenas-Pinto, A Palfreeman, F Post, D Ishola. **European Collaborators**: J Arribas, B Colebunders, M Floridia, M Giuliano, P Mallon, P Walsh, M De Rosa, E Rinaldi, S Bertagnolio, J Perriens; **Trial Steering Committee**: J Weller (Chair), C Gilks, J Hakim, A Kangewende, S Lakhi, E Luyirika, F Miiro, P Mwamba, P Mugyenyi, S Ojoo, N Paton, S Phiri, J van Oosterhout, A Siika, S Walker, A Wapakabulo; **Data Monitoring Committee**: T Pelo (Chair), N French, J Matenga; **Pharmaceutical companies**: G Clohertу, J van Wyk, M Norton, S Lehrman, P Lamba, K Malik, J Rooney, W Snowden, J Villacian. **The EARNEST trial was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP)** with contributions from the Medical Research Council, UK, Institito de Salud Carlos III, Spain, Irish Aid, Ireland, Swedish International Development Cooperation Agency (SIDA), Sweden, Instituto Superiore di Sanita (ISS), Italy and Merck, USA. Substantive in-kind contributions were made by the Medical Research Council Clinical Trials Unit, UK, CINECA, Bologna, Italy, Janssen Diagnostics, Mechelen, Belgium; GSK, UK; Abbott Laboratories, USA. Trial medication was donated by AbbVie, Merck, Pfizer, GSK and Gilead. WHO provided funding in partial support of baseline resistance testing.