Current First-Line Regimens are Effective in Patients With Single Transmitted TAM

Claire M.F. van Nispen tot Pannerden[1], Abdelilah el Barzouhi[1], Ard I. van Sighem[2], Jan M. Prins[3], Suzanne Jurriaans[4], Nicole K.T. Back[4], Kees Brinkman[5], Annemarie M.J. Wensing[6], Charles A.B. Boucher[7], Marchina E. van der Ende[1], Martin Schutten[7]

[1]Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands [2]Stichting HIV Monitoring, Amsterdam, The Netherlands [3]Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Amsterdam [4]Department of Virology, Academic Medical Center, Amsterdam [5]Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam [6]Department of Virology, University Medical Center Utrecht [7]Department of Virology, Erasmus MC, Rotterdam, The Netherlands

BACKGROUND: Currently the most prevalent transmitted resistance-associated mutations in Western European countries are Thymidine Analogue Mutations (TAMs). We hypothesize that in contrast to previously published data these mutations do not affect the efficacy of currently recommended first line combination antiretroviral therapy (cART) regimens with a low barrier to resistance development (GBR) (two NRTI and one NNRTI). This study analyzes the effect of transmitted single TAMs on efficacy of these regimens.

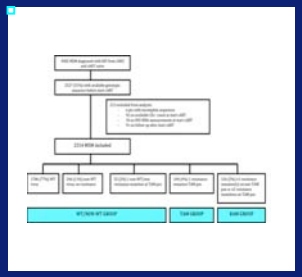
METHODOLOGY Patients included in this study were selected from the ATHENA national observational HIV cohort in the Netherlands.[1] The study population includesd all cART naïve MSM diagnosed in 2002 or later. PI and RT sequence was available at baseline. Patients were classified into three groups: (1) a single resistance-associated mutation on a TAM position (‘**TAM group**’), (2) a single resistance mutation on a non-TAM position or ≥2 resistance mutations on a TAM position (‘**RAM group**’), and (3) no resistance or only non-wildtype mutations (‘**WT/non-WT**’). The TAM group comprised MSM with a single resistance mutation on a TAM position (RT 41, 67, 69, 70, 210, 215, 219). Resistance-associated mutations were defined according to Bennet et al.[3]

cART regimens were classified as having a low or a high GBR. Genetic susceptibility scores (GSS) were assessed according to the methodology of Frentz et al.[4] A fully active regimen was defined as a regimen with GSS ≥3, a regimen with full resistance to all drugs in the regimen had a GSS of zero.

Patients were followed from the start of cART till the earliest of (i) the time of virological failure, (ii) treatment discontinuation/interruption lasting >2 wks, (iii) the time of the last RNA measurement, or (iv) 64 wks after start of cART.

VF was defined as the first of <1 $\log_{10}$ decrease in HIV RNA 4-8 weeks after start of cART compared to the pre-cART level, <2 $\log_{10}$ decrease after 8-16 weeks, or >200 cps/mL after 16 wks. Time to VF was analyzed using proportional hazards models., adjusted for age, CD4-cell count and HIV-RNA load at start of cART, period of starting cART and for GBR of the first-line regimen.

RESULTS



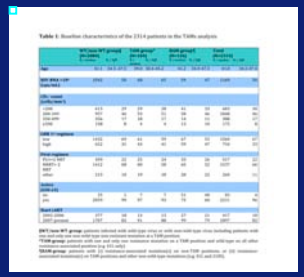
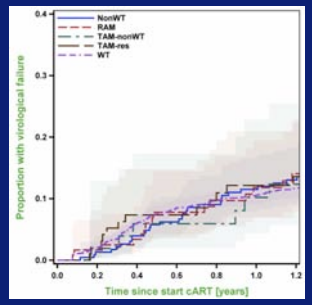
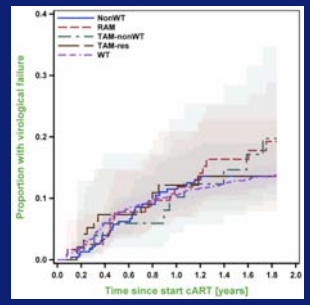


Table 2: Relative hazards for VF by subgroup relative to patients without resistance-associated mutations (‘WT’ or ‘non-WT’). Results are adjusted for viral load, CD4 count, age at start cART, and year of start. Threshold for VF defined as >200 cps/mL.

Time after start cART	64 weeks			96 weeks		
	RH	95% CI	p	RH	95% CI	p
2NRTI + 1 NNRTI (N=1537)						
Number failing	**154**			176		
RAM active§	0.61	0.15-2.47	0.5	0.79	0.25-2.44	0.7
RAM resistant*	2.82	1.32-6.08	0.008	2.60	1.21-5.58	0.01
TAM/¶	1.26	0.59-2.70	0.5	1.10	0.51-2.35	0.8
TAM/m‖	1.12	0.60-2.07	0.7	1.26	0.73-2.18	0.4
2NRTI + 1 PI/r (N=517)						
Number failing	**63**			70		
RAM active	0.35	0.05-2.49	0.3	0.32	0.04-2.31	0.3
RAM resistant	0.70	0.10-5.08	0.7	1.29	0.31-5.36	0.7
TAM/r	0.79	0.24-2.56	0.7	0.75	0.23-2.40	0.6
TAM/m	0.55	0.17-1.77	0.3	0.51	0.16-1.63	0.3
High GBR (N=754)						
Number failing	**92**			100		
RAM active	0.37	0.09-1.52	0.2	0.52	0.16-1.67	0.3
RAM resistant	1.55	0.56-4.26	0.4	1.84	0.74-4.57	0.2
TAM/r	0.79	0.32-1.97	0.6	0.75	0.30-1.86	0.5
TAM/m	0.82	0.30-1.79	0.6	0.77	0.35-1.68	0.5

§‘RAM active’: RAM group starting with fully active regimen (GSS ≥3)
*‘RAM resistant’: RAM group starting with not fully active regimen (GSS <3)
¶TAM/r: TAM group with resistance mutation
‖TAM/m: TAM group with resistance or non-wild-type mutation.





RESULTS: Of the 2314 diagnosed MSM, 104 (4%) were in the TAM group (97 (93.3%) full active regimen), 126 in the RAM group (5.4%), 75 (59.5%) of them with a fully active regimen. In total, 246 (11%) patients experienced VF.

Compared to patients in the WT/non-WT group, the hazard for VF was not different for the TAM group (relative hazard [RH] 0.95 (95% CI 0.52-1.75, p=0.9) or for RAM with a fully active regimen (RH 0.61, 0.25-1.48), but was higher for RAM with a non-fully active cART regimen (GSS <3) (RH 2.21, 1.20-4.06. p=0.01). Other covariates associated with VF were a CD_4^+-count of <200 cells/mm^3 at start of cART (RH 2.14, 95% CI 1.12-4.11, p=0.02) and a pretreatment HIV-RNA load of <10^5 copies/mL (RH 0.52, 95% CI 0.40-0.69, p<0.001)

In 1537 (66%) patients starting on 1 NNRTI + 2 NRTI, RH for VF was 1.26 (95% CI 0.59-2.70, p=0.5) in the TAM group, 0.61 (0.15-2.47; p=0.5) in the RAM group with fully active cART, and 2.82 (1.32-6.08; p=0.008) in the RAM group with non-fully active cART compared to WT/non-WT.

No differences were observed for patients starting high GBR regimens. Pretreatment viral load <105 cps/mL was associated with lower hazard of VF compared to ≥10^5 cps/mL (RH 0.52, 95% CI 0.40-0.69, p=<0.001).

CONCLUSIONS: The presence of a transmitted single TAM does not affect the efficacy of currently used first-line cART regimens.

REFERENCES

1. Stichting HIV monitoring report 2013. Ard van Sighem, Luuk Gras, Anouk Kesselring et al. First edition; November 2013. Sally H. Ebeling, Boston, MA, USA. ISBN/EAN: 978-94-90540-04-3.
2. van Sighem AI, van de Wiel MA, Ghani AC, et al.; ATHENA Cohort Study Group. Mortality and progression to AIDS after starting highly active antiretroviral therapy. . AIDS. 2003;17(15):2227-36.
3. Bennett DE CR, Otelea D, Kuritzkes DR, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One. 2009;4(3):e4724.
4. Frentz D BC, Assel M, De Luca A, et al. Comparison of HIV-1 genotypic resistance test interpretation systems in predicting virological outcomes over time. PLoS One. 2010;5(7):e11505 1-9.