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The demise of multidrug resistant HIV-1

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Background

- Despite a decreasing mortality and morbidity in treated HIV-1-patients, highly active antiretroviral treatment (HAART) can still fail due to the development of drug resistance.
- Especially multidrug resistant (MDR) virus poses a threat to efficient therapy.
- We studied the changing prevalence of MDR over time in a cohort of HIV-1-infected patients in Portugal.

Research Question:

Do the current treatment strategies still select for multidrug resistant HIV-1?

Material & Methods

- A Portuguese resistance database having more than 8000 HIV-infected patients from 22 hospitals in Portugal was used
- 10286 sequences for 8065 HIV-1 infected patients with at least one drug resistance test from July 2001 up to April 2012
- REGA algorithm version 8.0.2 was used to predict the susceptibility to drugs
- MDR at a specific date of sampling was defined as no more than one fully active drug at that time authorised by the National Authority of Medicines and Health Products (INFARMED). See figure 1.
- A generalized linear mixed model (GLMM) was used to study the time trend of the prevalence of MDR, taking into account the correlation among multiple samples per patient.
- Prevalence of MDR in a certain time interval = the proportion of patients with MDR respectively among those who had at least one sample for resistance testing in that time interval.
- Prevalence per 2 years was modelled over time and graphically visualized using a (univariate) Poisson regression model. See figure 2.
- Model adjusted for those confounding factors for which there was data available:
  - duration on therapy
  - incomplete initial start date of therapy
- data were analyzed using the free statistical software R

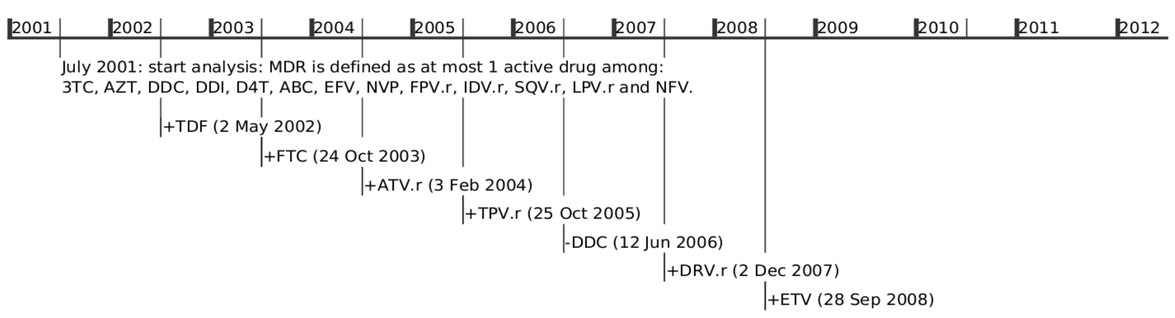

Figure 1. Overview of anti-HIV drugs used in the definition of multidrug resistance (MDR) based on dates of authorisation by INFARMED, the Portuguese National Authority of Medicines and Health Products. A virus was defined to be MDR at a specific date of sampling, when no more than one drug of this list was still fully active at that time point.

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Results

- decrease in prevalence of MDR over the last decade:
  - 6.9% [5.7-8.4] in 2001-'03
  - 6.0% [4.9-7.2] in 2003-'05
  - 3.7% [2.8-4.8] in 2005-'07
  - 1.6% [1.1-2.2] in 2007-'09
  - 0.6% [0.3-0.9] in 2009-'12

- Time: odds on MDR decreases with 17% per year in 2001-2012 (OR = 0.83 [0.82-0.84]; p<0.001)
- Duration on therapy: odds on MDR increases with 23% per year more on therapy (OR = 1.23, [1.21-1.24]; p < 0.001)
- Patients with an incomplete initial start date of therapy (n=1148, 14.2%): odds on MDR increases by 167% (OR= 2.67, [2.41-2.96]; p < 0.001)

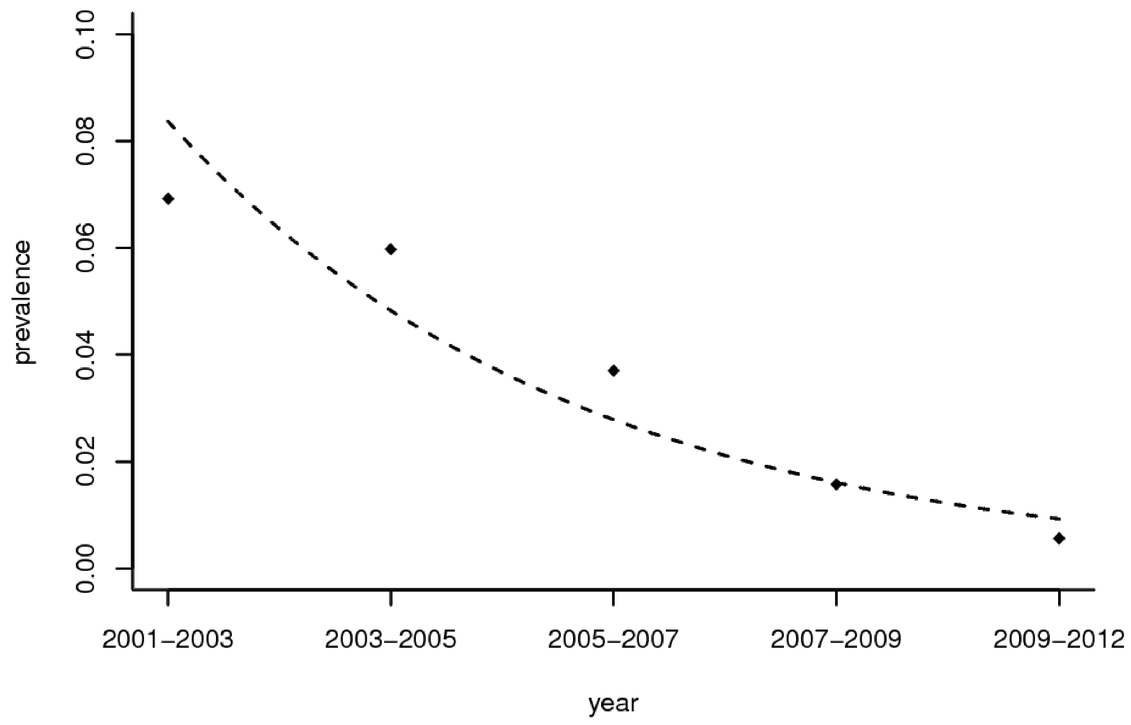

Figure 2. Time trend of prevalence per 2 years of multidrug resistant HIV-1 in Portugal. The prevalence in a certain 2-years interval was calculated as the proportion of patients with MDR respectively among those who had at least one sample for resistance testing in that time interval. Time trend was graphically visualized using a (univariate) Poisson regression model (dashed line).

Conclusions

Multidrug resistance decreased over time in Portugal:

- follows the improving therapy- and drug resistance testing strategies in high-income countries
- extrapolated to other countries where treatment of HIV-1 has been available from the late eighties
- drug developers are encouraged to focus more on better tolerability and ease of use of the drug instead of developing potent antiretroviral agents targeted at overcoming resistance
- remark: the following drugs were not taken into account and can still exhibit antiviral activity:
  - maraviroc (MVC, not for all patients information on viral tropism was available)
  - enfuvirtide (T-20, no resistance information on gp41 available)
  - raltegravir (RAL, not for all patients integrase genotype was available)
  - rilpivirine (RPV, no rules for this newest drug yet available in the REGA algorithm)

Last new case with MDR seen in July 2011 : Is our work on HIV drug resistance less necessary? No, because :

- several drugs that are still showing (high) prevalence of (novel) drug resistance anno 2012
- ongoing transmission of drug resistance : newly infected patients may already have drug resistant virus
- increasing antiretroviral resistance in lower-income settings