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The proportion of individuals without further treatment options has stabilized at low levels in the Swiss HIV Cohort Study (SHCS)

Background

- Knowledge of emerging patterns of HIV-1 drug resistance is of public health concern because studies have linked prevalence in the population of treated HIV-1 patients with transmission of drug resistant viruses during infection, thus jeopardizing treatment success of firstline therapy.
- Estimates of HIV-1 drug resistance prevalence amongst antiretroviral therapy (ART) exposed patients are challenging, because comprehensive cross-sectional analyses are not feasible and estimates based on drug resistance tests from routine clinical practice tend to be biased towards patients who experienced problems on antiretroviral treatment.

Objectives

- Aim 1: To estimate drug resistance prevalence of International AIDS Society - USA (IAS) mutations in ART-experienced patients, including the study population without on-treatment drug resistance tests available.
- Aim 2: To estimate the proportion of patients without further options for a standard two class regimen, consisting of two fully active NRTI drugs and either an NNRTI or a PI drug.

Methods

Study population/inclusion criteria for on-treatment analysis:

ART-experienced patients enrolled in the Swiss HIV Cohort Study (SHCS) with at least one study visit after January 1999.

Definition of virological failure (one of the following):

- viral rebound after suppression to <50 copies/mL with two consecutive viral loads >500 copies/mL
- one value >500 copies/mL followed by a stop or a modification of the current therapy
- exposure to mono or dual drug NRTI therapy for >30 continuous days

SHCS resistance database:

The SHCS resistance database contains all HIV resistance tests performed by the four laboratories authorized by the Federal Office of Public Health in Switzerland, stored in SmartGene's (Zug, Switzerland) Integrated Database Network System (IDNS version 3.5.0). Once detected mutations were assumed to persist (carry-forward).

Data analysis and statistics:

Aim 1: Estimation of drug resistance prevalence

Patients active in a given year were classified into four pre-specified groups:

- Patients with drug resistance mutations confirmed by genotypic testing (R group),
- Patients with prior virological failure or exposure to single or dual drug NRTI therapy (VF group),
- Patients who always maintained viral loads of <50 copies/mL on therapy (M50 group), defined as 2 successive HIV RNA below the cut-off in a year on the same therapy.
- Remaining patients were classified as having an unknown status (U group).

Based on available genotypic tests, the risk for the presence of at least 1 IAS drug resistance mutation was calculated for each group except R, where the probability was 1 by definition. Prevalence was then estimated as the frequency-weighted average of group-specific probabilities of resistance

- for groups VF, M50 and U (upper estimate),
- respectively for groups VF (in those patients without genotypic resistance test) and R (lower estimate).

Methods (continued)

Aim 2: Proportion of patients without further standard therapy options and success to salvage therapy

Standard regimens usually consist of 2 out of 4 NRTI groups (AZT/d4T; 3TC/ETC; ddI/ABC; TDF) and either a PI or an NNRTI. Patients on fusion inhibitors or therapies containing drugs not registered by the end of 2006 were excluded from this analysis.
Availability of future standard treatment options was assessed with

- the genotypic approach: In patients with genotypic resistance tests performed after initiation of ART, drugs with a Stanford genotypic sensitivity score >15 were considered non-active.
- the treatment history approach: Drugs as part of a virologically failing treatment were considered no longer effective. Cross-resistance was assumed within each NRTI group, within all NNRTI, and, if failure occurred on unboosted PI, within all PI except darunavir/tipranavir.

Therapy success, defined as 2 successive HIV RNA <50 cps/mL on the same treatment per calendar year, was compared between patients without further options based on the two approaches defined above and two reference populations, which were patients with confirmed triple class failure or triple class resistance and patients who had never experienced a virological failure event.

Results

Aim 1

- According to our classification, of 5997 patients active in 2007,
  - 1411 (23.5%) patients had ever had a resistance test indicating the presence of IAS mutations (group R)
  - 1345 (22.4%) patients had been exposed to mono/dual drug NRTI therapy or had experienced a virological failure (group VF).
  - 2459 (41.0%) patients had always maintained HIV RNA <50 copies/mL on therapy (group M50)
  - 782 (13.0%) had an unknown status (group U)
- The probability for the presence of resistance mutations was estimated at
  - 79.7% [95%CI 77.9-81.3] (n=2139 tests) for group VF
  - 27.4% [95%CI 23.2-32.1] (390) for group M50 and
  - 38.6% [95%CI 32.3-45.5] (207) for group U.
- Prevalence of drug resistance in ART-exposed patients was estimated at 49.7% [lower estimate] and 60.6% [upper estimate] for 1999, respectively 37.5% [lower] and 52.1% [upper] in 2007 (fig. 1)
  This decrease was driven by (table 2): Accelerated loss to follow-up/death of patients exposed to single class NRTI therapy (drug resistance prevalence in 2007: 75% [lower], 77% [upper]) and continued enrolment of patients with low risk profile because of therapy initiation with cART containing boosted PI or NNRTI (11% [lower], 35% [upper]).

Table 1: Characteristics of patients included in analysis.

	N (%)
Number of ART-exposed patients seen between 01/1999 and 12/2007	7861 (100.0)
Sex: female	2456 (31.2)
Age at first visit (median [IQR])	38 [33 to 44]
Ethnicity	
White	6261 (79.6)
Asian	243 (3.1)
Black	908 (11.6)
Hispanic	163 (2.1)
Unknown	286 (3.6)
Mode of HIV acquisition	
Heterosexual	2986 (38.0)
IV drug use	1862 (23.7)
Male having sex with male	2705 (34.4)
CDC stage C event	2275 (28.9)
Type of initial regimen	
Historic ART	3035 (38.6)
cART	1919 (24.4)
potent cART	2907 (37.0)
Ever exposed to mono/dual drug NRTI therapy or failed virologically	3690 (46.9)
Ever had a genotpyic drug resistance test	2613 (33.2)
Any NNRTI mutation	798 (10.2)
Any NRTI mutation (incl. M184V/I)	1255 (16.0)
Any PI mutation	875 (11.1)
≥1 resistance mutation	1814 (23.1)
Resistance against ≥2 classes	1126 (14.3)
Resistance against 3 classes	364 (4.6)

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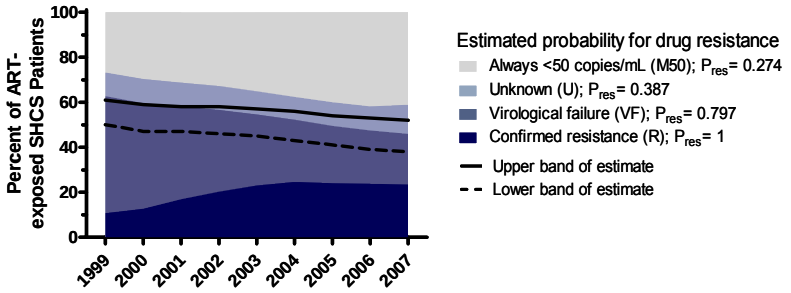
Figure 1: Classification of ART-experienced patients according to their risk for harbouring drug resistant viruses

Intensity of shading corresponds to likelihood for presence of resistance mutations: darker shaded areas indicate high-risk populations (confirmed drug resistance mutations [group R], respectively mutations very likely due to exposure to single class NRTI therapy or virological failure, [group VF]). The light shaded area represents patients who had always maintained HIV RNA <50 copies/mL on therapy [group M50] and who were thus at low risk for the emergence of resistant viruses.
Upper and lower prevalence estimates were calculated as the frequency-weighted average of group specific probabilities for drug resistance under varying assumptions.



Aim 2:

Proportion of patients without further standard options (fig. 2A)

- Genotypic approach: increase from 8% in 1999 to 13% in 2004, and stable levels since then.
- Treatment history approach: 33% between 1999 and 2001, followed by a drop to 11% in 2002 and stable since then. This sharp drop in 2002 coincided with the introduction of TDF.

Response to salvage therapy in 2007 (fig. 2B)

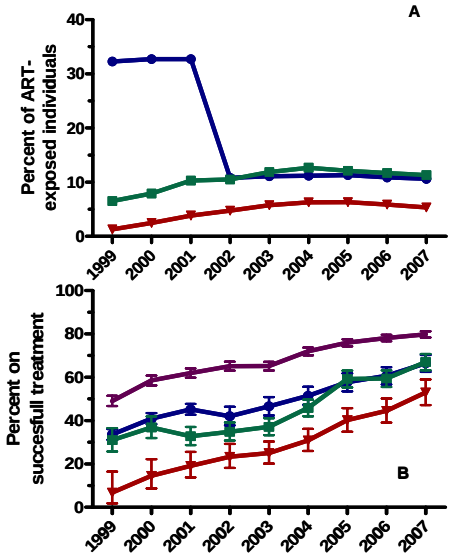
- Genotypic approach: 67.0% [95%CI 63.2-70.7]
- Treatment history approach: 66.4% [95%CI 62.4-70.3]
- Triple class failures/triple class resistance: 53.1% [95%CI 47.2-58.9]
- No prior virological failure (reference group): 79.8% [95%CI 78.3-81.2]

Table 2: Factors associated with loss to follow up and death.

	Still active in 2007	Loss to follow-up	Deaths	p
N	5772 (100.0%)	1284 (100.0%)	805 (100.0%)	
Sex: Female	1804 (31.3%)	444 (34.6%)	208 (25.8%)	<0.001
Age at last follow-up visit	44.0 [39.0-50.0]	39.0 [34.0-45.0]	43.0 [38.0-51.0]	nd [1]
Mode of HIV acquisition				<0.001
Heterosexual	2287 (39.6%)	498 (38.8%)	201 (25.0%)	
IV drug use	1060 (18.4%)	427 (33.3%)	375 (46.6%)	
Male having sex with male	2182 (37.8%)	319 (24.8%)	204 (25.3%)	
Other	243 (4.2%)	40 (3.1%)	25 (3.1%)	
Region of origin				<0.001
Northwestern Europe	4164 (72.1%)	833 (64.9%)	683 (84.8%)	
Sub-Saharan Africa	606 (10.5%)	186 (14.5%)	20 (2.5%)	
Southern Europe	458 (7.9%)	132 (10.3%)	61 (7.6%)	
Latin America	182 (3.2%)	55 (4.3%)	9 (1.1%)	
South- and East Asia	173 (3.0%)	21 (1.6%)	7 (0.9%)	
Eastern Europe	96 (1.7%)	25 (1.9%)	13 (1.6%)	
Other	93 (1.6%)	32 (2.5%)	12 (1.5%)	
CDC stage C event (ever)	1538 (26.6%)	313 (24.4%)	424 (52.7%)	<0.001
Type of initial therapy				<0.001
Historic ART	2038 (35.3%)	536 (41.7%)	461 (57.3%)	
cART	1331 (23.1%)	387 (30.1%)	201 (25.0%)	
potent cART	2403 (41.6%)	361 (28.1%)	143 (17.8%)	
Last available CD4 count (median [IQR])	481.0 [336.0 to 678.0]	371.0 [231.5 to 567.0]	180.0 [65.0 to 349.0]	nd [1]
Ever had a virological failure	1774 (30.7%)	466 (36.3%)	404 (50.2%)	<0.001
Ever had a genotypic test	1947 (33.7%)	392 (30.5%)	274 (34.0%)	<0.001
Ever any IAS mutations	1348 (23.4%)	256 (19.9%)	211 (26.2%)	0.032

[1] CD4 count and age were included as possible confounders and modeled as cubic splines with knots at 25th, 50th and 75th percentiles.

Figure 2: Patients without further standard therapy options and their response to salvage therapy



Panel A: Proportion of antiretroviral therapy-experienced population with no further standard treatment options based on treatment history (blue line), Stanford genotypic drug resistance score (green line), or triple class resistance/triple class failure (red line).

Panel B: Proportion of patients on successful salvage therapy, defined as 2 consecutive HIV RNA <50 copies/mL on the same treatment in the same calendar year.

Individuals without standard therapy options based on ...

- treatment history,
- genotypic resistance tests or
- virological failure on all classes or triple class resistance.
- Patients who have never failed virologically (Panel B only)

Conclusions

Drug resistance still represents a significant problem in highly treated populations, which, in the setting of a well developed health care system, has become more manageable over time.
This however probably does not hold true for developing countries, where fewer drugs and less means for monitoring virological failure and resistance development are available. Efforts to monitor the respective development have to be put high in the agenda of scale up antiretroviral treatment.

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