Round table discussion
Patients with multiresistant virus: A limited number, but a remarkable deal

Introduction

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History of multidrug resistant HIV

- In the pre-HAART era, multidrug resistant HIV emerged as a result of sequential, partially suppressive regimens.[1,2]
- Combination ART transformed HIV into a manageable condition, but early suboptimal 3-drug regimens led to continued selection for resistant HIV[2,3]
  - Low-potency ARVs with adherence challenges due to toxicity[3]
  - Cross-resistance within drug classes[3,4]
- Improved efficacy of modern ARVs has led to even less resistant HIV[2,5-7]
  - Expansion of ARVs and ARV classes allows for virologic suppression in patients with multidrug resistant HIV via informed use of combination regimens[4]

Emergence of acquired HIV-1 drug resistance has almost been stopped in Switzerland: a 15 year prospective cohort analysis


Background: Drug resistance is a major barrier to successful antiretroviral treatment (ART). Therefore, it is important to monitor time trends at a population level.

Methods: We included 11,084 ART-experienced patients from the Swiss HIV Cohort Study (SHCS) between 1999 and 2013. The SHCS is highly representative and includes 72% of patients receiving ART in Switzerland. Drug resistance was defined as the presence of at least one major mutation in a genotypic resistance test. To estimate the prevalence of drug resistance, data for patients with no resistance test was imputed based on patient's risk of harboring drug resistant viruses.

Results: The emergence of new drug resistance mutations declined dramatically from 401 to 23 patients between 1999 and 2013. The upper estimated prevalence limit of drug resistance among ART experienced patients decreased from 57.0% in 1999 to 37.1% in 2013. The prevalence of three-class resistance decreased from 9.0% to 4.4% and was always <0.4% for patients who initiated ART after 2006. Most patients actively participating in the SHCS in 2013 with drug resistant viruses initiated ART before 1999 (59.8%). Nevertheless, in 2013, 94.5% of patients who initiated ART before 1999 had good remaining treatment options based on Stanford algorithm.

Conclusion: HIV-1 drug resistance among ART-experienced patients in Switzerland is a well-controlled relic from the pre-combination ART era. Emergence of drug resistance can be virtually stopped with new potent therapies and close monitoring.
Prevalence of drug resistance among treatment experienced patients in North Carolina, by calendar year.

- **Graph Description:**
  - Panel B: Proportion with resistance over calendar time from 2000 to 2014.
  - Lines represent:
    - At least 1 class
    - At least 2 classes
    - At least 3 classes

- **Key Observations:**
  - In our cohort, the prevalence of drug resistance has declined in the last decade.
  - Resistance prevalence is very low for patients who initiated antiretroviral therapy in the modern treatment era.

- **Textual Content:**
  - Evaluation of resistance to at least 1, 2 or 3 drug classes among protease inhibitors, nucleoside and non-nucleoside reverse transcriptase inhibitors, integrase inhibitors over the years 2000-2014.

*Davy T et al., CROI 2017, abstract N° 483*
Resistance in ART-experienced patients significantly decreased from 1999 to 2010 in conjunction with a remarkable increase of GRTs without resistance.

Prevalence of resistance to any drug-class among ART-experienced HIV-1 infected patients over the years.

Analysis performed on 12660 sequences of protease, reverse transcriptase or integrase, from drug-experienced HIV-1 infected patients (N=6051). P-values by Chi-squared test for trend; statistically significant tests (p<0.05) are indicated in boldface. Sequences performed from 1999 to 2001 were grouped.

Armenia et al., European Meeting on HIV & Hepatitis 2017, Abstract # 69

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Armenia et al., European Meeting on HIV & Hepatitis 2017, Abstract # 69
After 2008, INI-resistance contributed to resistance mostly in those GRTs with ≥3 class resistance.

Analysis performed on 1529 protease/reverse transcriptase/integrase sequences from plasma samples of drug-experienced HIV-1 infected patients (1100). 703/1529 sequences had no drug-class resistance. P-values by Chi-squared test for trend. *Update August 2016. INI: integrase inhibitor.
Multidrug Resistant HIV (MDR) Still a Significant Concern in HIV

- Despite modern ARV combination regimens revolutionizing the treatment of HIV, **MDR HIV remains relevant**

- Due to cross-resistance within a drug class, fully active ARV options diminish with each successive viral failure

- Patients harboring MDR HIV pose increased risk of drug-resistant virus transmission

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Clinical Case: ID 18209 Patient infected with HIV-1 B subtype

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Risk Factor</th>
<th>1st Seropositivity</th>
<th>CDC stage</th>
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<td>F</td>
<td>Heterosexual</td>
<td>April 2017</td>
<td>A2</td>
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- **GRT (April 2017)**
  
  VL: 86,000 cps/ml  
  CD4: 476 cells/mm³  
  Subtype B  
  Therapy status: drug-naïve  

  Resistance mutations  
  PI: L63P  
  NRTI: T215S  
  NNRTI: V108VI E138G H221Y M230L  
  INT: G140S Q148H  
  Tropim: R5 (FPR: 46.5%)

- **GRT (October 2016)** (from a patient infected with a virus phylogenetically related)
  
  VL: 160,100 cps/ml  
  CD4: 202 cells/mm³  
  Subtype B  
  Therapy status:  
  May 16 - January 17: ETR RAL  

  Resistance mutations  
  PR: L63P  
  NRTI: T215S K219KE  
  NNRTI: V108VI E138G H221Y M230L  
  INT: G140S Q148H  
  Tropim: R5 (FPR: 46.5%)

Other mutations  
PR: L19V I62V E65D H69N  
INT: K34KR T124N M154L V201I T206S I208L
Transmission of HIV with integrase inhibitor (INI) resistance is so far very rare.


However, because of the increasing INI-usage in clinical practice, a recruitment to monitor integrase resistance in drug-naïve patients is mandatory in turn to improve both surveillance of transmitted INI resistance and individualization of first-line ART.
Conclusions

A dramatic drop of drug-resistance has been achieved, confirming a good clinical practice and ensuring a high number of treatment options for failing patients.

However, in the last 5 years drug-resistance is stable, and resistance to ≥3 classes remains a clinical relevant issue.

For the management of multi-class resistance an effort in the use of diagnostic tools is mandatory to ensure the efficacy of the currently available drugs.

In this frame, the development of new drugs and new drug classes is needed.