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TREATMENT STRATEGIES & ANTIVIRAL DRUG RESISTANCE
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Disclosure statement:
Dr. Santoro reports personal fees from ViiV Healthcare, Gilead and JANSSEN Cilag

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]

1. Lima VD, et al. Am J Epidemiol. 2010;172:460-468. 2. Richman DD. Clin Infect Dis. 2016;62:1318-1319. 3. Harris M, et al. AIDS Res Treat. 2012;2012:595762. 4. Tang MW, et al. Drugs. 2012;72:e1-e25. 5. Scherrer AU, et al. Clin Infect Dis. 2016;62:1310-1317. 6. Paquet AC, et al. Antivir Ther. 2014;19:435-441. 7. Davy T et al., CROI 2017, abstract N° 483.

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

Alexandra U. Scherrer, Viktor von Wyl, Wan-Lin Yang, Roger Kouyos, Jürg Böni, SabineYerly, Thomas Klimkait, Vincent Aubert, Matthias Cavassini, Manuel Battegay, Hansjakob Furrer, Alexandra Calmy, Pietro Vernazza, Enos Bernasconi, Huldrych F. Günthard, and theSwiss HIV Cohort Study

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

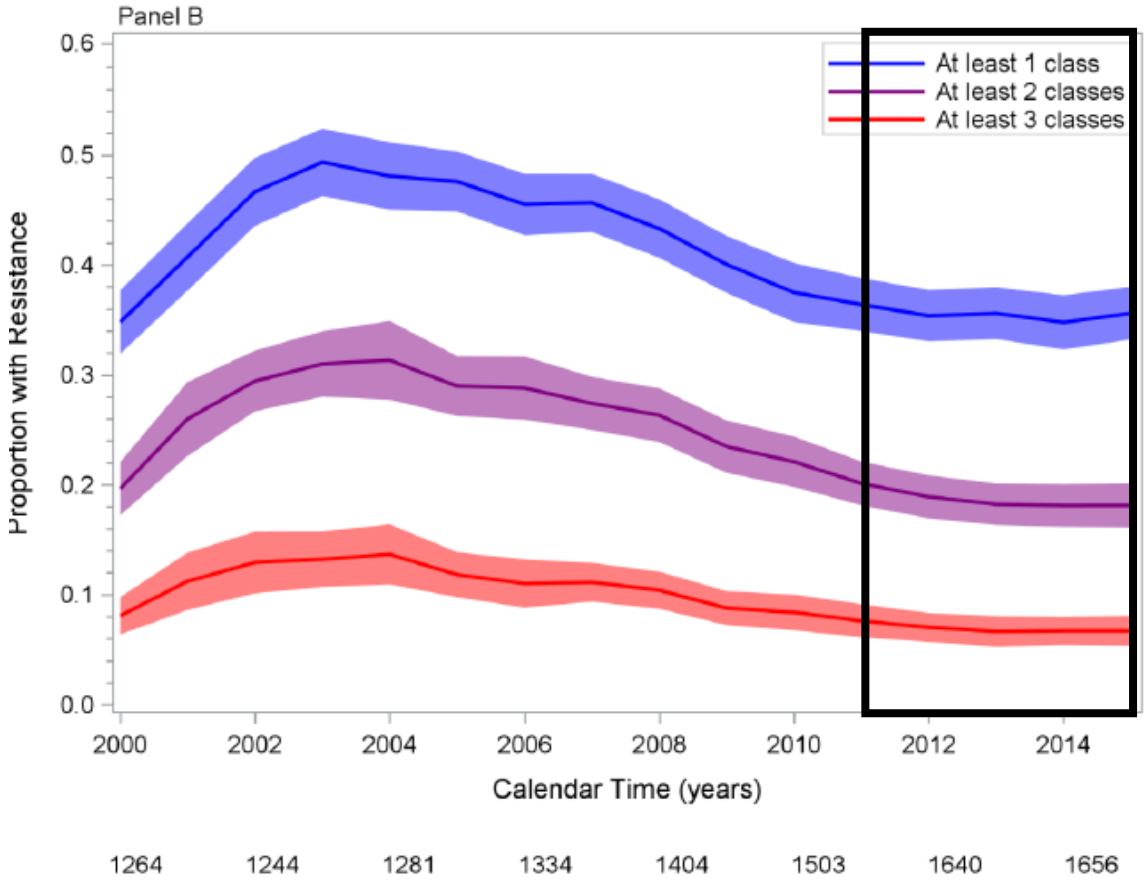
Methods: We included 11,084 ART-experienced patients from the Swiss HIV Cohort Study (SHCS) between 1999 and 2013. The SHCS is highly representative and includes 72% of patients receiving ART in Switzerland. Drug resistance was defined as the presence of at least one major mutation in a genotypic resistance 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.**

Clinical Infectious Diseases published March 8, 2016

Prevalence of drug resistance among treatment experienced patients in North Carolina, by calendar year.



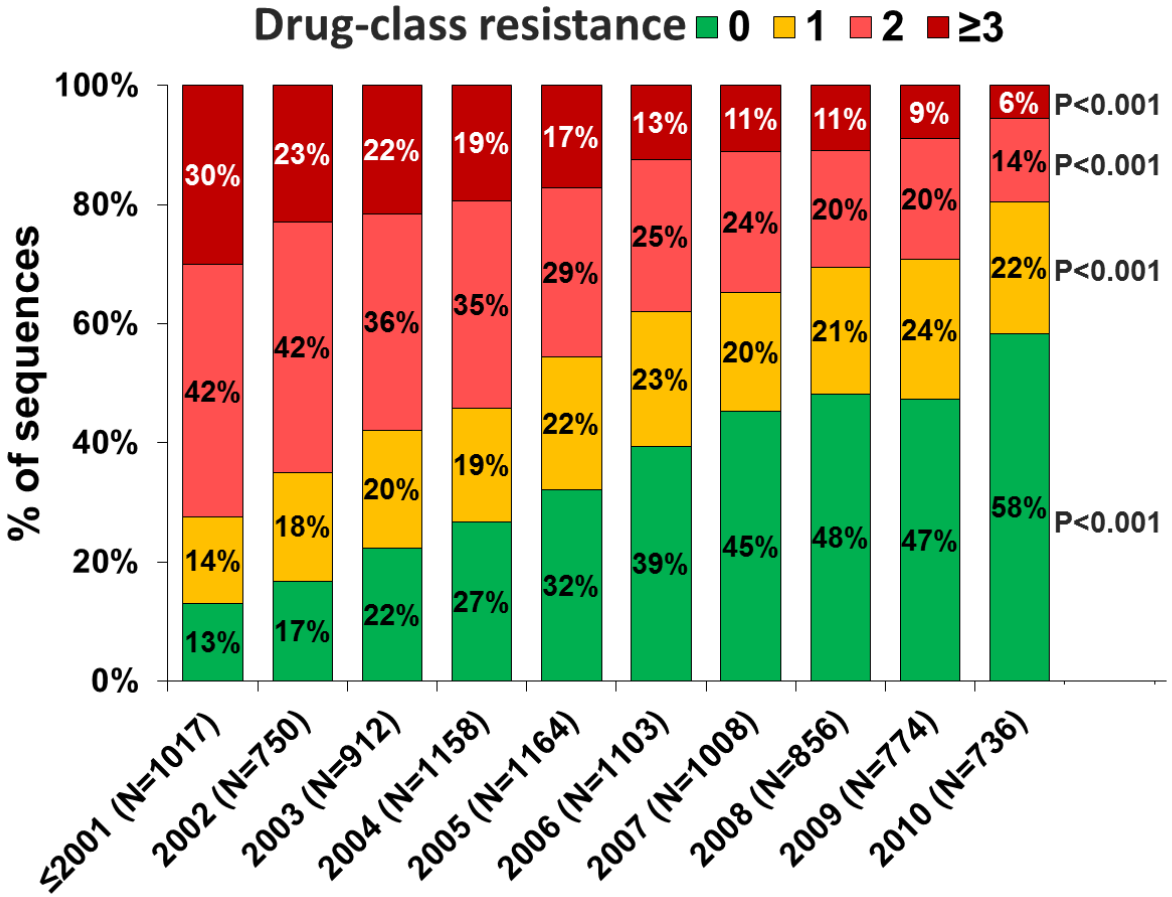
- In our cohort, the prevalence of drug resistance has declined in the last decade.
- Resistance prevalence is very low for patients who initiated antiretroviral therapy in the modern treatment era.

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.

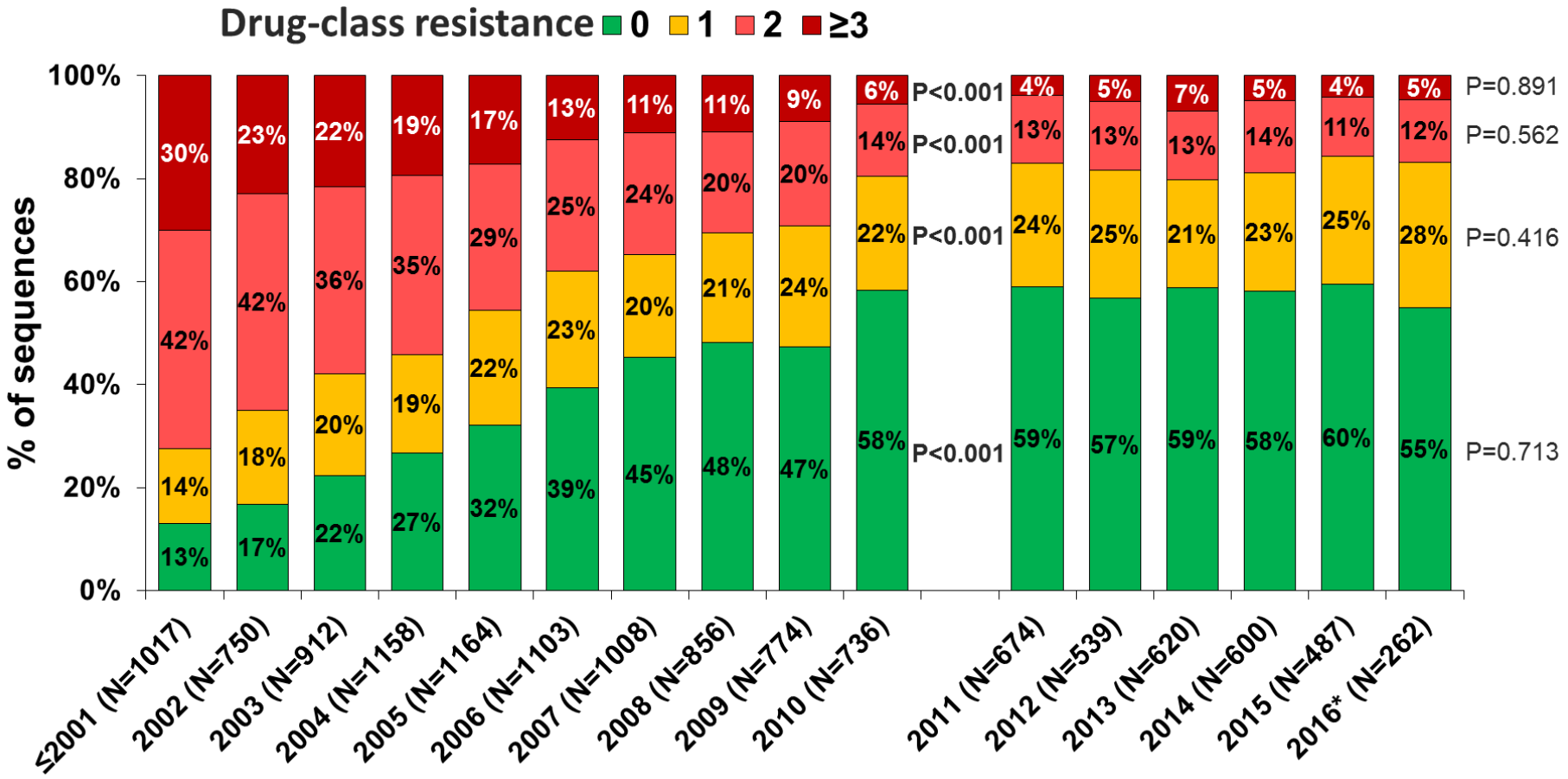


Analysis performed on 12660 sequences of protease, reverse transcriptase or integrase, from drug-experienced HIV-1 infected patients (N=6051). P-values by Chi-squared test for trend; statistically significant tests ($p<0.05$) are indicated in boldface. Sequences performed from 1999 to 2001 were grouped.

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

Beyond 2010, prevalence of resistance remained stable from 2011 to 2016.

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



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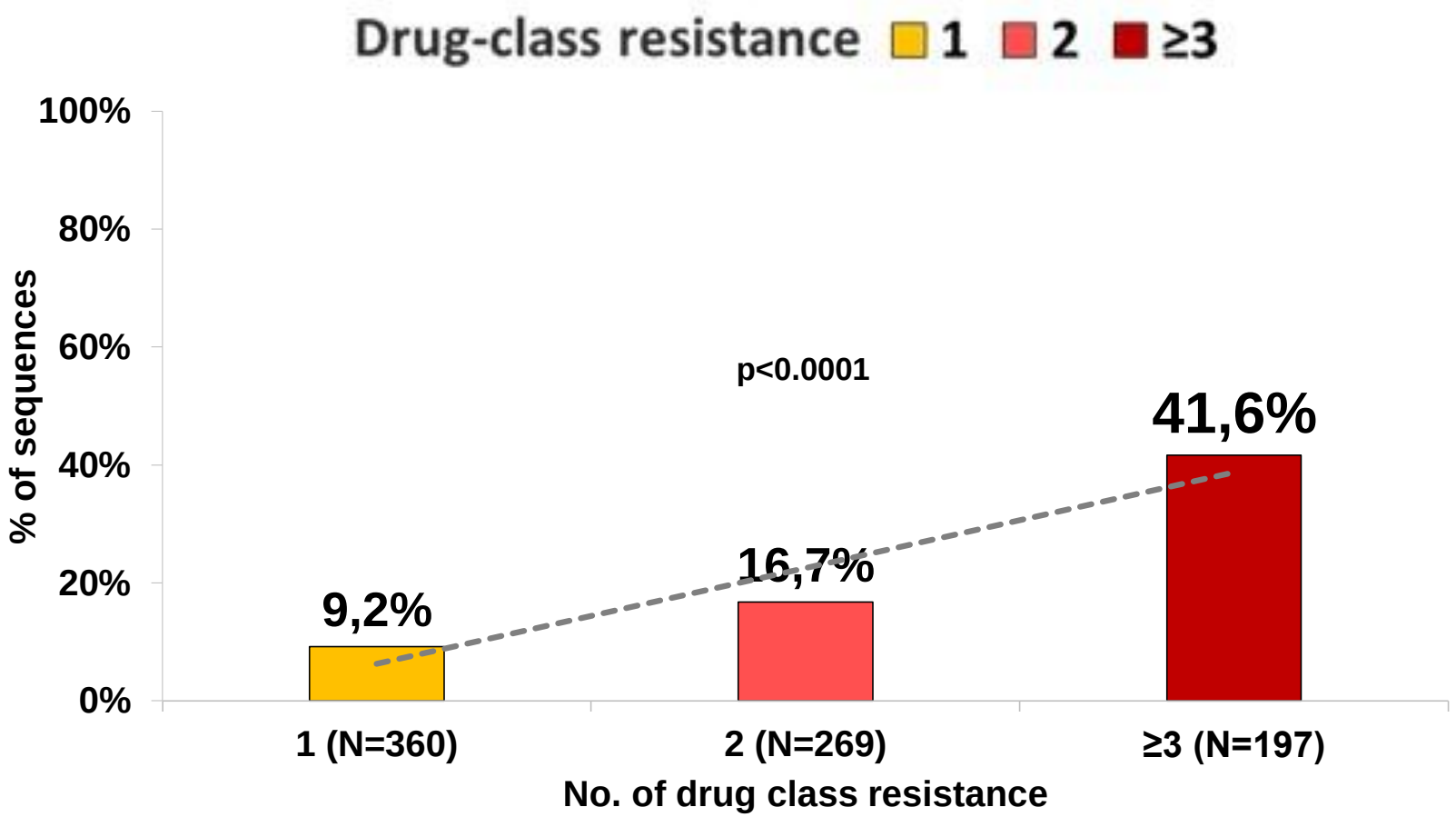
Armenia et al., European Meeting on HIV & Hepatitis 2017, Abstract # 69

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.

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

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

Tang MW, et al. Drugs. 2012;72:e1-e25. Imaz A, et al. AIDS Rev. 2011;13:180-193.
Lima VD, et al. Am J Epidemiol. 2010;172:460-468

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Clinical Case: ID 18209 Patient infected with HIV-1 B subtype	Age 36	Sex F	Risk Factor Heterosexual	1st Seropositivity April 2017	CDC stage A2

• **GRT (April 2017)**

VL: 86,000 cps/ml
CD4: 476 cells/mm^3
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%)

Other mutations
PR: L19V I62V E65D H69N
RT: K46Q V60I L109M V118I D123E I142K S162C I178L V179I G196E F214L A272P K277R R284K T286A I293V P294A E297R
INT: K34KR T124N M154L V201I T206S I208L

• **GRT (October 2016)** (from a patient infected with a virus phylogenetically related):

VL: 160,100 cps/ml
CD4: 202 cells/mm^3
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 I62IV E65D H69N
RT: K46KQ V60I S68SG V106VI L109LV V118I D123E I142K S162SC I178L G196E F214L L234LI A272P K277R R284RK T286A I293V P294A E297R
INT: VM50MV K111KQ T124N M154MIL V201VI T206TS I208L

Transmission of HIV with integrase inhibitor (INI) resistance is so far very rare.

- *Young B, et al. Antivir Ther. 2011; 16(2):253–256.*
- *Boyd S, et al. Antivir Ther. 2011; 16(2):257–261.*
- *Hurt CB. Antivir Ther. 2011;16(2):137-40.*
- *Bertoli A, et al. European HIV clinical forum 2016. Submitted.*
- *Hernandez AL, et al. CROI 2017. Abstract N° 478.*

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.