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worrying increase in ADR and PDR against NNRTI and also to some extent nucleos(t)ide RTI is not halted, it could jeopardize benefits achieved in resource limited settings (RLS) and could result in imported resistant viruses in RRS. A change in treatment strategy to integrase inhibitor (InSTI) based treatment regimens as initial but also for switch and in treatment failing individuals is a valid option to decrease ADR and PDR at least for some time. If this switch to InSTI based therapies, however, will not be accompanied by improved monitoring strategies including plasma RNA and resistance testing, success of such changes may only turn out to be of transient nature. To lay the ground for an evaluation of these issues I will discuss in this talk the benefits of HIV drug resistance testing for (i) individualized ART considering the fact that ART needs to be taken lifelong, (ii) for special populations, (iii) for surveillance of TDR/PDR and ADR also in the light of migration and (iv) for molecular epidemiology and timing of infection for informing public health.

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Integrase-based first-line HIV antiretroviral treatment in the Mediterranean Resistance (MeditRes) HIV collaboration

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Background and objective: Integrase strand-transfer inhibitor (INSTI)-based regimens are preferred regimens for first-line antiretroviral therapy in Europe. Our objective has been to study the prevalence of transmitted drug resistance to the INSTIs and the NRTI backbone in newly diagnosed patients that are naïve to ART.
Patients and methods: MeditRes HIV is a consortium that includes ART-naïve people living with HIV that have been newly diagnosed in France, Greece, Italy, Portugal and Spain during the years 2018 and 2019. Reverse transcriptase (RT) and integrase were sequenced following standard methodologies in use at the participating centres. To evaluate the prevalence of surveillance drug resistance mutations (SDRM) we used the Calibrated Population Resistance (CPR) tools for integrase and RT available at Stanford HIV website. To evaluate clinically relevant transmitted resistance, we used the Stanford HIVdb algorithm v8.9-1.
Results: Overall, we included 1844 patients with integrase and RT data available. At diagnosis, 79% were men, 72% of them were men that have sex with men, median age was 40 (IQR 30 to 54) years and median viral load was 104 000 (IQR 22 409 to 415 000) copies/mL; 47.2% of patients were infected by HIV-1 non-B subtypes. In particular, the most prevalent non-B subtypes were: CRF02_AG (20.0%), A (6.2%), C (4.6%), F (4.6%) and CRF01_AE (1.7%). The prevalence of INSTI SDRMs was 0.22% (T66I, n = 1; T66A, n = 1; E138T, n = 1; and R263K, n = 1). The prevalence of NRTI SDRMs was 3.6% (M184V, n = 16, 0.86%; K65R, n = 2, 0.1%; any STAMs, n = 45, 2.44%). Clinically relevant resistance, defined as any resistance level for Stanford interpretation ≥3, was 2.45% for INSTIs (0.05% to dolutegravir and bictegravir; 2.4% to raltegravir; 2.4% to elvitegravir), and 1.68% to the components of the NRTI backbones (0.76% to TDF/TAF; 1.46% to abacavir; 0.97% to lamivudine/emtricitabine).
Conclusions: Here we describe the most recent data on transmitted drug resistance to integrase-based first-line regimens in Mediterranean Europe. Given the low prevalence of clinically relevant resistance to second-generation INSTIs and to first-line NRTIs, in the years 2018 and 2019 it is very unlikely that a newly diagnosed patient in MeditRes countries would present with baseline resistance to a first-line regimen based on second-generation INSTIs.

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Impact of multi-drug resistance on mortality: a multi-cohort Italian study

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Background: In the past decades, HIV+ patients harbouring multidrug resistant (MDR) virus seemed to have an increased mortality, but recent data considering the new ART scenario are lacking.
Methods: The analysis included data of HIV+ patients of a retrospective multi-cohort study (Icona Foundation cohort, ARCA database and anonymous databases of Italian clinical centres). In order to account for variation in the frequency of genotype resistance test (GRT) across cohorts, both Stanford GSS v8.9 and previous history of virological failure on specific drugs (VFscore) were combined to estimate the rate of loss of drugs as future options. At each month, NRTI class was considered active if GSS and/or VFscore ≥2; NNRTI, PI, MVC, T20 if GSS and/or VFscore ≥1; and INSTI if GSS and/or VFscore ≥1.5. MDR at each month of follow-up was defined as currently having ≤2 active drug classes among drugs available for use. Poisson analysis

Abstract O323-Table 1. Rates, crude and adjusted relative rates (95% CI) of death (a) and of composite endpoint of AIDS diagnosis/death (b) from fitting a Poisson regression model in overall population and after stratification by calendar period

a)	Rates of death			Relative rates			
	Deaths	PYFU	Rates per 100 PYFU (95% CI)	Unadjusted		Adjusted[a]	
Current calendar period							
1996 to 2007	572	70666	0.81 (0.75, 0.88)	1.00		1.00	
2008+	760	147220	0.52 (0.48, 0.55)	0.64. (0.57, 0.71)	<.001	0.57 (0.48, 0.68)	<.001
1996 to 2007							
MDR							
No	442	55698	0.79 (0.72, 0.87)	1		1	
Yes	130	14968	0.87 (0.73, 1.03)	1.09 (0.90, 1.33)	0.366	1.62 (1.24, 2.12)	<.001
2008 to 2019							
MDR							
No	756	146965	0.51 (0.48, 0.55)	1		1	
Yes	4	255	1.57 (0.59, 4.18)	3.05 (1.14, 8.15)	0.026	2.43 (0.60, 9.80)	0.213

b)	Rates of composite outcome of AIDS/death			Relative rates			
	AIDS/deaths	PYFU	Rates per 100 PYFU (95% CI)	Unadjusted		Adjusted[b]	
Current calendar period							
1996 to 2007	393	62535	0.63 (0.57, 0.69)	1		1	
2008+	584	109139	0.54 (0.49, 0.58)	0.85 (0.75, 0.97)	0.014	0.87 (0.72, 1.06)	0.169
1996 to 2007							
MDR							
No	304	49109	0.62 (0.55, 0.69)	1		1	
Yes	89	13426	0.66 (0.54, 0.82)	1.07 (0.85, 1.36)	0.570	1.39 (1.00, 1.92)	0.051
2008+							
MDR							
No	580	108950	0.53 (0.49, 0.58)	1		1	
Yes	4	190	2.11 (0.79, 5.62)	3.97 (1.48, 10.60)	0.006	3.24 (1.03, 10.17)	0.044

[a]Adjusted for age, gender, nationality, mode of HIV transmission, HBV/HCV coinfection status, AIDS diagnosis, CD4 and HIV/RNA- at enrolment and year of enrolment;
[b]adjusted for age, gender, nationality, mode of HIV transmission, HBV/HCV coinfection status, CD4 and HIV-RNA at enrolment and year of enrolment.

was used for crude and adjusted relative rates (aRR) for death and for a composite endpoint of AIDS or death.
Results: Of 31 445 patients, 5954 (19%) were MDR. Median age was 38 (IQR 32 to 46), year of enrolment/diagnosis 2008 (2003 to 2013), calendar year of MDR 2003 (1999 to 2005). One thousand, three hundred and thirty-two deaths were observed over 217 886 person-year-follow-up (PYFU): 134 among MDR patients (IR 0.88 per 100 PYFU, 95% CI 0.74 to 1.04), 1198 among no-MDR (IR 0.59, 95% CI 0.56 to 0.63). MDR patients globally had a higher rate of death after the adjustment for potential confounders (aRR 1.67, CI 1.31 to 2.13). A lower RR of death was observed after 2008 (aRR 0.57, CI 0.48 to 0.68) in comparison with 1996 to 2007 period. Both in 1996 to 2007 and in ≥2008 calendar period, MDR patients had a higher aRR of death (aRR 1.62, CI 1.24 to 2.12, $p < 0.001$ and 2.43, CI 0.60 to 9.80, $p = 0.213$, respectively) versus no-MDR (Table 1a). In 25 084 patients evaluated for the composite endpoint AIDS/death, 5257 (21%) were MDR. MDR patients globally had a higher rate of AIDS or death (aRR 1.24, CI 0.93 to 1.67), confirmed also in the two calendar periods: 1.39 (CI 1.00 to 1.92) in 1996 to 2007 aRR and 3.24 (CI 1.03 to 10.17) after 2008 (Table 1b).
Conclusions: This retrospective study showed that despite a statistically significant decrease in mortality in HIV+ patients over time, those harbouring MDR are still burdened with higher disease progression and mortality.

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Lenacapavir resistance analysis in a phase Ib clinical proof-of-concept study

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Background: Lenacapavir (LEN, GS-6207) is a first-in-class subcutaneous (SC) long-acting inhibitor of HIV-1 capsid function, which can be administered every six months. *In vitro* resistance selections with LEN have identified seven mutations in HIV-1 capsid protein (CA) associated with reduced susceptibility to LEN, most with significantly reduced fitness. We conducted a phase Ib proof-of-concept study in which PLWH received a single SC injection of LEN 20, 50, 150, 450, or 750 mg. LEN demonstrated potent antiviral activity with up to 2.3 log10 decline in HIV-1 RNA after nine days of monotherapy. Here we describe the resistance analyses for all participants.
Materials and methods: Study 4072 is a double-blind, placebo-controlled, dose-ranging, randomized (3:1; n = 8/group) study in PLWH who were capsid inhibitor naive. Resistance analyses were performed for all participants prior to study entry and at the end of monotherapy using genotypic and phenotypic Gag-Pro assays (Monogram Biosciences) and next-generation sequencing (NGS; Seq-IT). Samples were