ABSTRACTS
Abstract #O_01
A Multicenter Observational Study on the Efficacy and Tolerability of Dolutegravir combined with Tenofovir/Emtricitabine or Abacavir/Lamivudine as a Switch Strategy for HIV-1 Positive, Antiretroviral-experienced Patients with Stable Viral Suppression

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Background: Dolutegravir is an integrase inhibitor (INI) with high efficacy and is recommended with two nucleoside reverse transcriptase inhibitors (NRTIs) in naïve, HIV-infected patients. Limited evidence is available about the use of dolutegravir-based regimens in treatment-experienced, virologically-suppressed patients.

Material and Methods: We estimated the rates of treatment failures (TF, discontinuation of dolutegravir for any cause) and virological failures (VF, 2 consecutive HIV-RNA>50 copies/mL or one HIV-RNA>1000 copies/mL) in a multicenter cohort of virologically suppressed, HIV-positive patients switching to dolutegravir plus either tenofovir/emtricitabine or abacavir/lamivudine. Predictors of TF were analyzed by Cox regression analysis. Changes in immunological, metabolic, renal and liver functions at weeks 24 and 48 were also analyzed and predictors of changes were identified by linear regression.

Results: One hundred and seventy-three participants (71.7% male, 41.6% heterosexual, median age 51 years) began dolutegravir combined with tenofovir/emtricitabine (n=66) or abacavir/lamivudine (n=107). Statistically significant differences between groups treated with tenofovir/emtricitabine and abacavir/lamivudine regarded: risk factor for HIV, prevalence of hepatitis B surface antigen, previous VF and type of NRTI employed before switch (76% of patients on tenofovir/emtricitabine vs 27% on abacavir/lamivudine switched from a tenofovir/emtricitabine-based regimen).

No VF was detected during 1090 patients-month of follow-up (FU). TF occurred in 16 (9.2%) participants. The Kaplan-Meier estimated probability of remaining on dolutegravir at week 8, 24 and 48 was 95.3% (95% confidence interval, CI, 93.4%-99.6%), 93.7% (95% CI 90.0%-97.4%) and 81.0% (95% CI, 71.0%-91.0%), respectively. The median time to TF was 81 days (interquartile range 18-246).

Reasons of TF were represented by: hypersensitivity reactions (2); gastro-intestinal events (1); liver toxicity (3); renal toxicity (1); neurological toxicity (6); drug interaction (1); unspecified intolerance to study drug (2). All events leading to TF were of mild-moderate severity.

A decrease in mean total cholesterol (TC) was evident in the whole population (-11 mg/dL, p=0.016 at week 24; -22 mg/dL, p=0.023 at week 48) but, after stratifying for backbone, it was confirmed only in tenofovir/emtricitabine group (-22 mg/dL, p=0.018 at week 24; -45 mg/dL, p=0.053 at week 48). The use of tenofovir/emtricitabine (vs ABC/3TC: -32 mg/dL; p=0.006) and higher baseline TC values (per 1 mg/dL more: -0.20 mg/dL; p=0.028) were independently associated with a greater reduction in TC at week 24, whereas the use of a tenofovir-containing regimen (versus other regimens: +22 mg/dL; p=0.043) or an INI-based regimen (versus other regimens: +20 mg/dL; p=0.049) before switching to dolutegravir were inversely related to a decrease in TC.

The same decreasing trend was shown for triglycerides (-17 mg/dL, p=0.031 at week 24; -24 mg/dL, p=0.040 at week 48), but also in this case the reduction was significant only in tenofovir/emtricitabine arm (-29 mg/dL, p=0.022 at week 24). An increase in mean creatinine levels (+0.07 mg/dL, p<0.001) was seen at week 24, without differences between backbones. CD4+ cell count and liver enzymes did not change over time.

Conclusions: Dolutegravir-based three drug regimens confirmed their high virological efficacy in this cohort. However, we detected a significant rate of dolutegravir discontinuation (9.2%), that prompts the need for extended follow-up studies.
Abstract #O_02

Efficacy of integrase strand transfer inhibitors in different HIV-1 subtypes

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*Equal contributions

Background: Dolutegravir (DTG) is a second generation HIV-1 integrase (IN) strand transfer inhibitor (INSTI). DTG (together with tenofovir and emtricitabine) is currently included in first-line antiviral treatment regimens in resource-rich settings. DTG has been shown to be a promising alternative to non-nucleoside reverse transcriptase inhibitors (NNRTIs) since its introduction in resource-limited sectors of the United States (downtown Washington, DC, the South Bronx, and downtown Los Angeles) in patients infected with HIV-1 subtype B (HIV-1B). However, its effect among patients from low- and middle-income countries, which mainly have non-B HIV-1 is poorly studied. In order to fill this gap, we cloned IN genes from patient isolates from HIV-1B, HIV-1C and CRF01_AE and determined inhibitory profiles of DTG in biochemical assays.

Methods: Patient-derived IN genes were cloned into the pRSFDuet plasmid to prepare recombinant IN proteins from different subtypes. All proteins were purified to near homogeneity using Ni-affinity chromatography. Gel-based assays were used for monitoring strand-transfer and 3’-end processing assays in the presence and in the absence of DTG. Synthetic template-primers (21-mer duplex and 19/21-mer partial duplex) were used for determining DTG binding affinity. Molecular models of IN-DNA complexes were generated for all subtypes. These models were then used for DTG docking to determine the binding energies of DTG in IN-DNA complex. Molecular models of IN-DNA complexes were generated for all subtypes. These models were then used for DTG docking to determine the binding energies of DTG in IN-DNA complex. All the therapy naïve chimeric viruses gave an EC50 fold change ≤1 compared to NL4-3 with EC50 values < 3nM.

Conclusion: Our biochemical, molecular modeling and virological data suggest that DTG binds to HIV-1C IN with slightly better affinity that to HIV-1B and 01_AE integrases. These results suggest that DTG can be a strong choice-drug for non-B HIV-1 subtype.
ABSTRACTS

Abstract #O_03
Virological failure even at low levels of viremia can be associated to integrase strand-transfer inhibitors resistance in HIV-1 infected patients

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Background: Treatment of HIV-1 infection with effective antiretroviral therapy (ART) reduces plasma viral load (VL) to undetectable levels measured with clinical assays. Some patients, however, experience a persistent low-level viremia (VL <200 copies/mL) or virological failure (VL >200 copies/mL). Genotyping resistance testing is not always possible to perform when HIV-1 VL is 50-1000 copies/ml and plasma ultracentrifugation is required prior to RNA extraction. Here, we report a case of a highly experienced HIV-1 infected patient with VL <200 copies/ml harboring resistance-associated mutations to raltegravir.

Materials and Methods: We report a clinical case of a highly experienced HIV-1 infected patient carrying historical multidrug resistance associated mutations with persistent low level viremia despite a salvage ART regimen based on raltegravir who is followed at the HIV Clinical Unit from the Hospital Universitari Germans Trias i Pujol (Barcelona, Spain). Two consecutive plasma VL <200 copies/mL were detected after 2 years on darunavir/ritonavir (600/100 mg BID) + raltegravir (400 mg BID) + maraviroc (150 mg BID) and sustained virological suppression. After evaluation of treatment adherence, tolerability, drug-drug and food-drug interactions, and psychosocial issues, a genotyping resistance test was performed by a plasma ultracentrifugation method. Prior to RNA extraction, virions were concentrated from 15-ml plasma samples. Then, HIV-1 genotyping of the reverse transcriptase (RT), protease (PR) and integrase genes, as well as HIV tropism were performed following standard procedures. Resistance-associated mutations and HIV tropism were assessed by Viroscore and Geno2pheno algorithms. Clinical resistance degree was determined by Stanford HIVdb algorithm.

Results: Patient’s tolerability and adherence to treatment regimen were good and no drug-drug or food-drug interactions were documented. The RT, PR, and integrase genes were successfully sequenced and revealed strains carrying T97AT mutation that conferred low-level resistance to raltegravir. Viral tropism was CCR5. A new salvage ART regimen was initiated with dolutegravir (50 mg BID) + darunavir/ritonavir (600/100 mg BID) + maraviroc (150 mg BID) and the VL was re-suppressed (VL <40 copies/mL).

Conclusions: The clinical case reported here illustrates that HIV-1 infected patients with virological failure at low levels of viremia can also harbor resistance-associated mutations to integrase strand-transfer inhibitors. Therefore, it is important to consider those cases for genotyping. The use of plasma ultracentrifugation may be helpful in this clinical setting.
Abstract #O_04

An Italian case of transmitted integrase inhibitor resistance in a drug-naive patient: a refined analysis by ultra-deep-454 pyrosequencing

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Background: Transmission of HIV with integrase inhibitor (INI) resistance is so far very rare. However, a recruitment to monitor integrase resistance in drug-naive patients is mandatory for the increasing INI-usage in clinical practice.

Materials & Methods: We describe a case of an Italian patient naïve to antiretroviral therapy (ART) infected with a multi-resistant HIV-1 strain. Protease, reverse transcriptase (RT) and integrase genotypic resistance tests (GRT) were performed before treatment starting, through both Sanger sequencing and 454 GS-Junior ultra-deep pyrosequencing (UDPS) in plasma, proviral DNA and cerebrospinal fluid (CSF) compartments. Resistance to protease inhibitors, RT inhibitors (RTIs) and INIs was evaluated by Stanford HIV Drug-resistance list 2015. Mutational-load (in plasma and CSF) was calculated per each resistance mutation. HIV-1 co-receptor usage was determined through gp120-V3-loop Sanger sequencing by using the geno2pheno algorithm (false positive rate [FPR %] set at 10%).

Results: A 45-years-old Italian man was diagnosed for syphilis and HIV-1 infection on February 2016 (last HIV test negative in 2014) with CD4-count of 567 cells/μl (CD4%: 24%) and viremia of 92,470 copies/ml. On March, plasma genotypic resistance test (GRT) revealed a F1 subtype X4-tropic virus (FPR 3.8%). Resistance to RTIs and INIs was evaluated by Stanford HIV Drug-resistance list 2015. Mutational-load (in plasma and CSF) was calculated per each resistance mutation. HIV-1 co-receptor usage was determined through gp120-V3-loop Sanger sequencing by using the geno2pheno algorithm (false positive rate [FPR %] set at 10%).

In proviral-DNA, primary RTI and INI resistance was detected exclusively through UDPS as minority quasi-species (M184V: 9.4%; N155H: 11.3%); T97A integrase mutation was found as major quasi-species (100%), while M184I (0.8%) and V179D (5.4%) RTI resistance mutations were detected as minority quasi-species.

At the same time point, in CSF, neither M184I/V nor N155H were detected trough both techniques. Differently, V179D (10.9%, mutational load: 2,336 copies/mL) was detected as minority quasi-species in RT and T97A (97%, mutational load: 20,784 copies/mL) was detected through both sequencing techniques. In June 2016 (HIV RNA: 144,500 copies/mL; CD4-count 633 cells/μl [CD4%: 23%]) the patient started a dual ART-regimen containing darunavir/ritonavir and etravirine. After 2 months (August 2016), HIV-1 RNA decreased to 688 copies/mL (viremia decay: -2.32 log10 copies/mL) and CD4-count was 635 cells/μl (CD4%: 26%).

Conclusions: Despite the current rarity of transmitted INI resistance, this patient is the first documented case in Italy. He harbored a transmissible amount of RTI/INI resistant virus circulating in plasma as major quasi-species. Resistant variants were already archived in proviral reservoir as minority quasi-species but they were completely absent in CSF compartment. This case underlines the importance of performing an integrase GRT in drug naïve patients in turn to improve both surveillance of transmitted INI resistance and individualization of first-line ART.
Abstract #O_05

French National survey of resistance to integrase inhibitors shows high differences of resistance selection rate in case of virological failure in a context of routine hospital care (ANRS AC11 virology network).

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Background: Integrase inhibitors (INIs) are now one of the most important drug classes in clinical practice. With potential for INI cross-resistance, there is a need to get more resistance data in patients failing an INI containing regimen in a context of routine hospital care. Doing so with more cases than observed in clinical trials to date would provide a more precise description about the robustness to resistance selection of the 3 INIs used in clinical practice.

Materials and methods: This national survey of resistance to INIs was conducted through the ANRS AC11 virology network: patients who failed to any INI containing regimens were included to search for selection of resistance to INI and associated factors. Virological failure was defined as 2 consecutive plasma viral load > 50 copies/mL. All the genotypic resistance tests were performed on the second plasma sample with detectable viral load and interpreted following the ANRS V25 algorithm. Patients who failed to RAL and EVG did not failed to any INI before. However, DTG was used either as the first INI or in patients who failed before to RAL or EVG.

Results: 489 patients failing to INI (270 to RAL, 111 to EVG and 98 to DTG) containing regimen were analysed (median age 48 years, CD4 398/mm3, Viral Load 3.13 log copies/ml at time of failure). In combination with one INI, 250 (51%) patients received 2 NRTIs, 34 (7%) 1 NNRTI, 47 (9%) 1 PI, 76 (16%) 1 NRTI + 1 PI, 19 (4%) 1 NRTI + 1 NNRTI, 22 (4%) 1 NNRTI + 1 PI and 41 other regimens.

Among patients failing to RAL, 32% harboured a virus resistant to RAL and among patients failing to EVG, 40% harboured a virus resistant to EVG. Among patients failing to DTG (used as the first INI or used in patients previously exposed to RAL or EVG containing regimen) 19% harboured a virus resistant to DTG. Among the 96 patients failing to DTG, 49 received DTG as the first INI, neither INI resistance mutations among the major pathways (92, 118, 121, 140, 143, 148, 155) nor the R263K mutation were present at failure.

Conclusions: in this national survey, RAL and EVG are associated with 32 to 40% resistance at failure. However, in INI naïve patients, failing to DTG when used as the first INI, no resistance to INI was detected whatever the antiretroviral associated to DTG.
Abstract #O_06

Virological response of HIV-infected-patients virologically-suppressed switching to a DTG-based regimen in an observational cohort based on the genotypic susceptibility score

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Background: To assess, in a clinical cohort of virologically-suppressed patients, the virological response after switching ARV-treatment to a dolutegravir (DTG)-based regimen based on the genotypic susceptibility score.

Materials and methods: A prospective observational single-center cohort enrolling all patients with a plasma viral load (pVL) <50 c/mL initiating a DTG-based regimen between September and December 2015. VL were performed using Cobas Taqman HIV-1 V2.0 assay. The Genotypic Susceptibility Score (GSS) of the antiretroviral regimen was calculated using the ANRS version 25 (September 2015) algorithm including DTG, translating the interpretations “susceptible”, “possible resistance” and “resistance” into susceptibility scores of 1, 0.5 and 0, respectively.

Results: Among 254 patients who switched to a DTG-based regimen, 209 had historical available genotypes. Among them, taking into account all historical genotypes, 27 (13%), 61 (29%) and 121 (58%) had a GSS equal to 1 or 1.5, 2 and 3, respectively. Median time since last genotype was 9, 9 and 5 years in the 1 or 1.5, 2 and 3 GSS strata, respectively. Patients’ characteristics at time of DTG-based regimen initiation were different according to the GSS, as depicted in the table. At W24, 7 patients (3.3%) discontinued DTG-based regimen: neuro-psychological side effects (n=1), cutaneous side effects (n=1), pregnancy (n=1), renal toxicity (n=1), headaches (n=1) and patients’ decision (n=2). At W12, 95%, 96% and 95% of the patients had pVL <50 c/mL in the 1 or 1.5, 2 and 3 GSS strata, respectively. At W24, 100%, 96% and 96% of the patients had pVL <50 c/mL, in the 1 or 1.5, 2 and 3 GSS strata, respectively. Among the 12 patients (11.9%) displaying a pVL >50 c/mL (median=102 c/mL, IQR=61-417), 9 experienced a viral blip, 1 a virological failure (VF) and in the two remaining patients no further control sample was available. The only one patient (1%) experiencing VF was highly pre-treated including a previous VF under a RAL-based regimen with no selection of integrase resistance mutations and with a GSS=3.

Conclusions: In this observational cohort, patients’ characteristics at time of switching to a DTG-based regimen were different depending on the GSS strata. However, short-term follow-up showed a high level of the maintenance of virological suppression, regardless to the baseline GSS. These data suggest that DTG remains potentially able to maintain viral suppression when combined with fully or incompletely active drugs in these longterm virologically-suppressed patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GSS = 1 or 1.5 (n = 27)</th>
<th>GSS = 2 (n = 61)</th>
<th>GSS = 3 (n = 121)</th>
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<tr>
<td>Male sex, n (%)</td>
<td>21 (78)</td>
<td>35 (57)</td>
<td>86 (71)</td>
</tr>
<tr>
<td>Age, median years (IQR)</td>
<td>51 (46-55)</td>
<td>53 (42-59)</td>
<td>51 (41-58)</td>
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<tr>
<td>Time since HIV diagnosis, median years (IQR)</td>
<td>21 (16-24)</td>
<td>20 (16-21)</td>
<td>13 (6-21)</td>
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<td>Duration of prior ART, median years (IQR)</td>
<td>17 (10-29)</td>
<td>18 (5-19)</td>
<td>11 (5-29)</td>
</tr>
<tr>
<td>Number of previous ART lines, median (IQR)</td>
<td>8 (5-10)</td>
<td>6 (2-7)</td>
<td>4 (2-7)</td>
</tr>
<tr>
<td>Duration of HIV-1 RNA &lt;50 copies/mL before switch, median years (IQR)</td>
<td>3 (2-7)</td>
<td>4 (2-5)</td>
<td>3 (1-5)</td>
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<tr>
<td>Baseline CD4 cell count, median cells/mm3 (IQR)</td>
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<td>645 (535-865)</td>
<td>570 (400-750)</td>
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<td>Nadir CD4 cell count, median cells/mm3 (IQR)</td>
<td>183 (53-269)</td>
<td>220 (204-306)</td>
<td>221 (85-325)</td>
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<td>Associated antiretroviral drugs, n (%)</td>
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<tr>
<td>ABC/3TC</td>
<td>19 (70)</td>
<td>4 (7)</td>
<td>75 (62)</td>
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<td>TDF/FTC</td>
<td>1 (4)</td>
<td>4 (7)</td>
<td>29 (24)</td>
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<tr>
<td>3TC</td>
<td>0 (0)</td>
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<td>0 (0)</td>
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<td>RPV</td>
<td>3 (11)</td>
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<td>0 (0)</td>
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<td>DRV/r + NRTI</td>
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<td>3 (5)</td>
<td>10 (8)</td>
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<td>Others ATV drugs</td>
<td>3 (11)</td>
<td>6 (10)</td>
<td>7 (6)</td>
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<tr>
<td>Number of NRTI drug resistance mutations, median (IQR)</td>
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<td>Number of M184V, n (%)</td>
<td>27 (100)</td>
<td>52 (50)</td>
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<td>Number of NRTI drug resistance mutations, median (IQR)</td>
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<td>Number of major PI drug resistance mutations, median (IQR)</td>
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<td>Time since last genotypic resistance test, median years (IQR)</td>
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<td>9 (5-14)</td>
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</table>
Abstract #O_07
Lamivudine plus either Atazanavir/ritonavir, Darunavir/ritonavir or Dolutegravir as switch strategies in HIV-positive, virologically-suppressed patients: a comparison

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Background: Dual therapies with lamivudine and boosted-PI represent effective simplification strategies in selected HIV-positive, virologically-suppressed patients. Recent observational studies have underlined the potential role of lamivudine with dolutegravir in this clinical setting but comparison studies among these strategies are lacking.

Materials and Methods: We compared the incidence of treatment failure (TF, the composite outcome of treatment discontinuation and/or virological failure, as defined by single HIV-RNA>1000 cp/ml or two consecutive HIV-RNA>50 cp/mL) at week 24 and 48 in a retrospective observational cohort of HIV-positive, virologically-suppressed patients, switching to lamivudine plus either darunavir/ritonavir, atazanavir/ritonavir or dolutegravir. A comparison of laboratory changes at week 24 and 48 among different groups was also performed.

Results: We analyzed 313 patients switching to lamivudine plus either darunavir/ritonavir (120), atazanavir/ritonavir (111), or dolutegravir (82). Main baseline characteristics were similar between groups: overall median age was 48 years, 73.8% were men, 15.3% HCV-Ab+, median nadir CD4 209 cells/µL, zenith HIV-RNA 4.86 log10 copies/mL, 56.5% had a history of virological failure and 11.8% past evidence of M184V. Significant differences between groups concerned: duration of antiretroviral therapy exposure, treatment type before switch (59.8% of patients switching to dolutegravir were already on a dual-therapy regimen) and reasons for switch (mainly simplification for patients on boosted-protease inhibitors, dyslipidemia for patients on dolutegravir). Kaplan-Meier estimates showed no differences at week 24 and 48 in the probability of remaining on darunavir/ritonavir (99.2% and 93.0%, respectively), atazanavir/ritonavir (98.2% and 94.6%) or dolutegravir (98.8% and 88.6%). One patient on darunavir/ritonavir experienced virological failure over 100.9 patients-year of follow-up (PYFU); 2 patients on atazanavir/ritonavir and 2 on dolutegravir had virological failure over 82.5 and 58.9 PYFU, respectively. Other causes of TF were: dyslipidemia (41.2%) or other toxicities (53.0%) in the darunavir/ritonavir group; further simplification (21.7%), renal (13.0%), gastro-intestinal (4.3%) and liver (8.7%) toxicities or unknown causes (21.7%) with atazanavir/ritonavir; neurological toxicities (25.0%) or unknown (50.0%) with dolutegravir.

An increase in total cholesterol (TC, +20 mg/dL; p<0.001), LDL (+15 mg/dL; p<0.001), triglycerides (+17 mg/dL; p=0.026), TC-to-HDL ratio (+0.37; p=0.009) at week 24 was found in the darunavir/ritonavir group; in atazanavir/ritonavir group, no change in triglycerides and a decrease of TC-to-HDL (-0.30; p=0.005) at week 48 was evident; in dolutegravir group, a decrease in both TC-to-HDL (-0.49; p=0.023) and triglycerides (-48 mg/dL; p=0.008) at week 48 and an increase in HDL-to-LDL (+0.04; p=0.030) at week 24 emerged. A significant difference in changes of TC-to-HDL ratio at week 24 was found between the dolutegravir group and both protease inhibitors-groups (p<0.001). At week 48, in dolutegravir group, an increase in serum creatinine (+0.07 mg/dL; p=0.047) was noticed, whereas in atazanavir/ritonavir group there was a significant increase in eGFR (+4 mL/min; p=0.016). A small increase in transaminases was also shown in dolutegravir group at week 24, whereas no differences in CD4 count changes emerged among groups.

Conclusions in this observational study: Lamivudine-based dual therapies confirmed good virological efficacy. Preliminary findings seem to suggest that a switch to dolutegravir/lamivudine could be taken into consideration in virologically-suppressed patients, especially those with issues of dyslipidemia.
Abstract #O_08

Switching from combination antiretroviral therapy (cART) to dolutegravir (DTG) monotherapy in virologically suppressed HIV-1 infected adults: a randomized multicenter, non-inferiority clinical trial (DOMONO).

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Background: DTG containing cART showed equal or superior viral suppression when compared with raltegravir, efavirenz, or darunavir containing cART and is one of the preferred regimens in current treatment guidelines. As short and long-term side effects of cART remain a concern, maintenance HIV therapy with fewer drugs is an attractive goal. Given, the high genetic barrier to resistance, DTG is a potential candidate for maintenance monotherapy.

Materials/methods: In a randomized open label multicenter study, we compared DTG maintenance monotherapy (50mg QD = DOLUMONO) with continued cART (= con-cART). After 24 weeks, the con-cART patients switched to DOLUMONO as well ("delayed switch"). Eligible patients were on cART and suppressed (<50c/ml) for >6months, had a CD4 nadir≥200cells/mm3, HIV-RNA zenith<100.000c/ml, had no history of virological failure (VF) and were HBV immune. The primary endpoint was the proportion of patients with virological suppression at 24 weeks defined as a viral load(VL)<200c/ml in the modified intention to treat population. With an anticipated viral suppression of 95% on con-cART, 104 patients were needed to demonstrate noninferiority of DOLUMONO (delta 0.12, power 80%, alfa=0.025). Predefined secondary endpoints were (1) proportion with a VL <50c/ml after 24 weeks of DOLUMONO versus con-cART and (2) proportion with a VL <200c/ml and <50c/ml after 12, 24 and 48 weeks of DOLUMONO in the entire study population (=immediate + delayed switchers combined). The study was registered as NCT02401828.

Results: The 104 patients included were predominantly male (91.3%), had a median age of 45 years, an HIV-RNA zenith of 21840c/ml (IQR 7045-59550), CD4 nadir of 340cells/mm3 (IQR 272-507) and were on cART for 40 months. 87 of 104 patients have passed the week 12 of DOLUMONO endpoint. 98% (85/87) had a VL < 200 c/ml and 97% (84/87) had a VL < 50 c/ml. One patient on DOLUMONO with virological failure had a VL at 4 weeks of 70,000c/ml despite 100% compliance by pill-count and therapeutic DTG plasma levels of 1.3mg/L. Integrase sequencing on stored pre-cART plasma and at DTG failure did not reveal resistance-associated mutations. The other patient with virological failure had a VL at 12 weeks of 678 c/ml. Further details are not available at the time of abstract submission but will be presented at the meeting. At week 12, 1 patient had discontinued DTG because of disturbed sleep.

Conclusions: In a carefully selected HIV-1 population on suppressive cART, DTG monotherapy was well-tolerated and non-inferior to cART. Although these results are promising, longer follow-up is of course essential. Week 24 results will be presented at the meeting.
Abstract #O_09

Maintenance Therapy with Dolutegravir/ Rilpivirin is efficient and well tolerated in a real-life setting

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Background: Triple therapy is standard of care in antiretroviral treatment. However in already well-suppressed patients dual regimens might be sufficient to maintain viral suppression and spare drug toxicities but also costs. Several dual therapies combining different antiretroviral agents are currently studied. In this single center retrospective analysis efficacy and tolerability of a dual therapy with dolutegravir (DTG) and rilpivirin (RPV) were evaluated.

Methods and results: 45 chronically HIV-1 infected patients were started on dolutegravir/ rilpivirin in the last three years. 2 patients (both with a very low baseline viral load) were therapy naive and thus excluded from further analysis. 43 patients were switched from a current cART. Median time on treatment is 11 months (1-29 months). All patients were virologically suppressed at the time of switching. Reasons for changing therapy were mainly adverse events of the current regiment, predominately affecting the renal function (21/43 pts) or therapy simplification (7/43 pts). Only three patients prematurely terminated therapy due to patient-reported adverse events after 3 weeks to 5 months of therapy, 40/43 patients remained on DTG/RPV until the end of the observation time. No virologic failure occurred and all patients were BLQ at the end of observation time.

Conclusion: Thus in this small, single center analysis a dual therapy consisting of DTG and RPV seems efficient and well-tolerated in a maintenance scenario.
Abstract #P_08
Analysis of pol gene region coding integrase in HIV-1 samples from nosocomial outbreaks in Russia in 2014-2016.

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Background: Since 1986 HIV-1 is spreading in Russia and in the end of 2015 one million HIV-infected patients was registered in our country. Since 2010 and until present time the main routes of infection are intravenous drug usage (55%) and heterosexual contacts (42%). However nosocomial HIV-1 outbreaks in Russia occur periodically. The most known case of nosocomial outbreak in USSR and Russia occurred in Southern Federal District in 1989. More than 250 people (mostly children) were infected by HIV-1 subtype G from Congo because of unsterile medical manipulation. Since 2007 more than 15 confirmed and suppositional cases of nosocomial outbreaks were registered in different Russian regions: in Central, North Caucasian, Southern, Volga and Ural Federal districts.

Each case of these outbreaks has been investigated. Nucleotide sequences of HIV-1 from people involved in outbreaks were analyzed using phylogenetic analysis for epidemiological relationships identification. The search of possible gene features in these sequences is carried out as well.

Two integrase inhibitors (INIs), raltegravir (RAL) and dolutegravir (DTG) are registered for treatment in Russia. Recently there was published data about high efficacious and good adherence to therapy in patients treated by these drugs. Analysis of gene pol region coding integrase in HIV variants circulating in Russia helps to evaluate the efficacious of INIs treatment in our country and reveal the polymorphism features of these variants.

Materials & Methods: We analyzed pol gene partial sequences (positions 4230-5090) coding integrase (IN) from ART-naïve patients from nosocomial outbreaks occurred in 2014-2016. The alignment of the sequences was performed with MEGA6.0 using algorithm ClustalW. Genotyping was carried out in on-line tools COMET HIV-1/2 and HCV v.0.2 and REGA HIV-1 Subtyping Tool v.3.0. The analysis of drug resistance mutations was carried out using HIVdb Program v.7.0.

Results: IN sequences from 89 HIV-1 samples from nosocomial outbreaks from Smolensk, 2014 (n=8), Bryansk, 2015 (n=10), Lipetsk, 2015 (n=23), Samara, 2015 (n=13), Ugra, 2015 (n=10), Ulan-Ude, 2016 (n=24) and Vologda, 2016 (n=1) were studied. 85 (95.5%) samples belonged to subtype A1 dominating in Russia. 81/85 viruses of subtype A1 harbored substitution L74I, polymorphism of subtype A1 variant dominating in Russia since the middle of 90-s. Only 2 samples from Smolensk and one sample from Samara were subtype B viruses. Also one sample from Lipetsk belonged to CRF02_AG.

All samples harbored gene features associated with INIs susceptibility were A1 viruses. Only one sample from Ugra harbored virus with high-level resistance to RAL associated with F121Y and Q146P mutations. One sample from Lipetsk had the virus with high-level resistance to RAL and eviletgravir (EVG) and intermediate resistance to DTG because of mutations Y143C, Q148H and S153F. Also one sample from Bryansk harbored viruses with mutation G163R which effect on resistance to INIs isn’t well studied.

Conclusion: We found very low rate (3.4%) of INIs resistance in collection studied. Study must be continued with addition analysis of viruses isolated from antiretroviral-treated but INI-naïve patients because viruses from these patients may harbor preexisting resistance to INIs.
Abstract P#_09

Safety and efficacy of dolutegravir in treatment-experienced subjects harboring HIV-type 1 strains highly resistant to first-generation integrase inhibitors

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Background. Dolutegravir (DTG), combined with an optimized antiretroviral background therapy (OBT), is promising for the treatment of multi-drug resistant (MDR) HIV and has been recently approved for adults and adolescents. Aim of this work was to analyze the efficacy and safety of this strategy in subjects infected by HIV type 1 strains highly resistant to first-generation integrase inhibitors in clinical practice.

Methods. Six subjects previously exposed to several antiretroviral regimens, including most of NRTIs, NNRTIs, PIs and Raltegravir, who failed previous therapies and harbored an MDR virus, between December 2011 and March 2016, started DTG 50 mg twice daily with OBT. Clinical events, CD4+ T cell counts, HIV-1 RNA load were analyzed at baseline and after one month and thereafter every three/four months. Changes of the initial OBT therapy were not considered.

Results. Median age was 50 (IQR 47-53), median years of HIV infection 20 (IQR 17-21), 50% were female, 5 (83.3%) had sexual transmission, 2 had AIDS diagnosis (33.3%), 5 (83.3%) had a Dual-Tropic virus. 6 (100%) subtype B virus, median CD4 nadir 232 (IQR 72-296) cells/mL. Median time on a failing regimen including raltegravir was 15 months (IQR 6.4-32). At baseline all subjects had genotypic evidence of INSTI resistance: 148H plus two mutations in four subjects, 148H plus 1 mutation in one, 143C plus 66I and 157Q in one; CD4 count was 345 (IQR 301-394), median HIV-1 RNA load 3.8 (IQR 2.7-4.3) Log10. Median follow up was 32 months (IQR 17-51). Antiretrovirals associated to DTG were: DRV/r+ETV+T20 in 3 subjects and LPV/r+MVC, LPV/r+TDF, DRV/r+ETV in the other 3. All patients but one reached undetectable HIV-1 RNA. A rapid antiviral response was observed in three subjects (60%) with less than 50 copies/mL at month 1. At week 24 and 48, 4/4 subjects in follow-up (100%) had less than 50 copies/mL. Two subjects with 2 and 4 years of follow up, respectively, maintained HIV-1 RNA <50 copies/mL. CD4 cell counts increased steadily: +43 (month 6), +88 (1 year), +140 (2 year), +215 (3 year), +203 (4 year).

Conclusion. Despite predicted resistance to all available INSTI, DTG 50 mg twice daily with an optimized background provided durable viro-immunological response in five of six patients with a history of multiple treatment failures and MDR virus. No patient interrupted DTG due to side effects.
Abstract #P_10
PK of FTC, TFV and 3TC in Ugandan and Nigerian Breastfeeding Mother-Infant Pairs

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Background: Increasing numbers of women receive anti-retroviral therapy (ART) throughout breastfeeding. Knowledge regarding the pharmacokinetics (PK) on nucleoside reverse transcriptase inhibitors (NRTIs) to breastfed infants is incomplete. Following assay development, we assessed intensive PK profiles of emtricitabine (FTC), tenofovir (TFV) and lamivudine (3TC) in maternal dried blood spots (mDBS), dried breast milk spots (DMS) and infant DBS (iDBS) from Ugandan and Nigerian cohorts.

Materials & Methods: Breastfeeding mothers receiving a once-daily efavirenz or nevirapine-based ART regimen were enrolled, together with their exclusively breastfed infants. Paired DBS (maternal and infant) and DMS were collected pre-dose and serially up to 12 h post-dose. All three NRTIs were quantified by a validated simultaneous LC-MS/MS assay. 3TC and TFV maternal plasma concentrations were measured in the Ugandan cohort, enabling derivation of a correction factor (based on the average ratio between plasma and mDBS) to standardise DBS for plasma concentrations. Non-compartmental PK analysis was performed using WinNonLin and DMS:mDBS ratios were calculated arithmetically.

Results: 21 Ugandan and 27 Nigerian mother-infant pairs were enrolled. Populations were similar for mean maternal age (30 years) and weight (60 Kg), and infant age (100 days) and weight (6 Kg). Tmax of FTC was 4 h in mDBS and 5.1 h in DMS, reaching median Cmax of 493 (IQR 467-627) and 933 (716-1238) ng/mL, respectively. The AUC0-12 of FTC was 2492 (511-3260) and 4134 (824-7286) ng.h/mL in mDBS and DMS, with a DMS:mDBS AUC ratio of 2.13 (SD 1.77). FTC was detectable in 18.7% of exposed infants with a median iDBS concentration 18.5 (SD 3.4) ng/mL.

TFV had a Tmax of 1 h in mDBS and 4 h in DMS, reaching Cmax of 186 (109-240) and 7.3 (5.5-9.6) ng/mL in these compartments, respectively. The AUC0-12 was 1014 (738-1394) and 41.5 (23.2-56.1) ng.h/mL in mDBS and DMS, giving a DMS:mDBS AUC ratio of 0.034 (SD 0.09). No infant had measurable TFV. 3TC had a Cmax of 991 (574-1129) ng/mL in mDBS and 572 (386-710) ng/mL in DMS. The AUC0-12 of 3TC in mDBS and DMS was 3916 (2985-6780) and 4001 (1951-4577) ng.h/mL, respectively, with a DMS:mDBS AUC ratio of 1.02 (SD 0.79). 3TC was detectable in 41% of exposed infants with a median iDBS concentration 16.4 (SD 8.5) ng/mL. Plasma and mDBS were strongly correlated for 3TC (R2=0.97) and TFV (R2=0.88), with the correction factor of correction factor of 0.88 for 3TC and 1.57 for TFV. Following correction, Bland-Altman analysis indicated good agreement between the two methods.

Conclusion: We have validated a method to quantify FTC, 3TC and TFV in DBS and DMS. This is the first report of full PK profiles of FTC and TFV in DBS and BM of breastfeeding mother-infant pairs, indicating higher concentration of FTC in BM compared to mDBS but transfer to iDBS only in a minority. TFV is measurable in BM but is not detectable in iDBS. Consistent with previous studies, 3TC levels in BM were comparable to mDBS with transfer to iDBS in almost half the infants.
Abstract #P_11

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The patient is a 58-year-old male, diagnosed with HIV infection in 1992. After diagnosis, he started treatment with azydohthimidine monotherapy and subsequently received dual nucleoside reverse transcriptase inhibitor (NRTI) and triple (NRTI + non-NRTI/protease inhibitor)-drug antiretroviral regimens.

He had been treated with all of the following: dideoxycytidine, dideoxyinosine, saquinavir/ritonavir, nelfinavir, nevirapine, abacavir, efavirenz, hydroxyurea, lopinavir/ritonavir, amprenavir, enfuvirtide, tipranavir, tenofovir(TDF), emtricitabine(FTC), darunavir/ritonavir(DR/r), etravirine, maraviroc(MVC) and raltegravir. He was included in several clinical trials. He participated in TORO study, with exposure to enfuvirtide and in DUET study (DR/r + Etravirine vs DR/Vr + placebo).

Despite a good adherence, patient did not achieve sustained virological suppression. According to the Stanford University HIV Drug Resistance Database interpretation algorithm, his bulk historical genotypes were interpreted as:
  - High-level resistance to all NRTI and NNRTI
  - High-level resistance to all protease inhibitors.
- Fusion inhibitor resistance: V38M, V38A, V38E.
  - Reduce enfuvirtide susceptibility by more than 10-fold in site-directed mutants and most clinical isolates.
- Integrase Inhibitor: E92Q, N155H, N155I.
  - High-level resistance to raltegravir and elvitegravir and low-level resistance to DTG.
- HIV tropism test performed in April 2009 (Trofile): CX4 tropic virus.
  - CCR5 inhibitors not active.

The patient had received many of the drugs in the antiretrovirals regimens as functional monotherapy. While receiving TDF/FTC+DRV/R+MVC, he presented oral candidiasis and wasting (CD4 cell count 28 cells/ml and HIV-RNA viral load 110000 copies/ml). On April 2011, the patient initiated DTG (50mg BID) through a compassionate use program, high-dose DRV/R (1000/100 mg BID), peg-interferon alfa-2a (PEG-IFN-a2a) (180mg weekly) and stavudine (d4T), TDF/FTC and enfuvirtide at standard doses. Rapid decrease in viral load, but no suppression, was observed. Several changes of drug doses and new drugs (foscamet and valaciclovir) were done to control viraemia and toxicities. Subsequently, the patient has been receiving DTG, high-dose DRV/r and MVC maintaining virological suppression for 32 months.

Immunological reconstitution, with important increased CD4 count, has been observed in the patient. Initial CD4 count was 24 cells/ml. CD4 count increased gradually as viral load was suppressed. An increased in CD4 count, 161 cell/ml, was observed after 21 months of treatment with DRV/r+DTG+MVC+PEG-IFN-a2a. After 20 months treated with DRV/r+DTG+MVC, CD4 count was 343 cells/ml and no new AIDS event were presented.

Last 12 months the patient has continued doing well, has not presented new AIDS events neither other complications and keeping virological suppression and immunological response (CD4 count has increased to 442cells/ml).
Abstract #P_12
Dolutegravir in combination with Darunavir/Cobicistat as second line ART: a case report

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Case Report
We report a case of a 43 year-old female patient, diagnosed in 2006 with HIV infection, B3 stage, with a CD4 cell count of 108 cells/mm3 and HIV-1 RNA 690,000 cps/ml. Her risk factor was heterosexual intercourse.

She refused antiretroviral therapy (ART) until October 2013, when she received Abacavir/ Lamivudine (ABC/3TC) 600/300 mg QD and Lopinavir/ Ritonavir (LPV/r) 400/100 mg BID, without virological suppression or immunological restoration. Adherence to treatment and visit attendance was poor and she reported nausea, diarrhea and weight loss.

In February 2015 her treatment was switched to Single Tablet Regimen, Tenofovir/ Emtricitabine/ Rilpivirine (TDF/FTC/RPV) 245/200/25 mg QD, to improve compliance, while HIV-1 RNA and CD4 cell count were 31,000 cps/ml and 141 cells/mm3, respectively. The patient reported an higher adherence rate, but she assumed therapy often without food.

In April 2016, when she was referred to our center, she had low body mass (BMI 18.7 kg/m2), oral thrush and multiple superficial lymphoadenopathy. HIV-1 RNA and CD4 cell count were 193,000 cps/ml and 103 cells/mm3, respectively. Estimated glomerular filtration rate (eGFR using CK-EPI) was 90 ml/min. Co-infections and other laboratory abnormalities were not detected. Genotypic resistance test revealed subtype B strain and multiple NRTI resistance mutations (K65R, Y115F, E138K, V179L, M184V, Y188L), without resistance to protease inhibitors or integrase inhibitors. The viral tropism performed on HIV-RNA was R5, with a False Positive Rate of 16. HLA*B5701 was negative. Bone densitometry showed hip and lumbar spine osteopenia. After the results, on 24 May 2016, she started ART including Dolutegravir (DTG) 50 mg QD in combination with Darunavir/ cobicistat (DRV/cobi) 150 mg QD.

After one month, on 21 June 2016, HIV-1 RNA was 172 cps/ml, CD4 cell count 236 cells/mm3 . She reported complete adherence, good tolerably and improvement of quality of life. Oral thrush was resolved and body weight increased. On 22 August 2016, HIV-1 RNA was <40 cps/ml, CD4 cell count 290 cells/mm3 , eGFR 92 ml/min.

An effective second line regimen is a challenge for patients who have been exposed to NRTI with first line ART failure and with several drug intolerances. In this short follow up, our case offers a clinical insight into the efficacy of combination of DTG and DRV/cobi in a difficult real-life setting. DTG+DRV/ cobi association could warrant high genetic barrier, good tolerability and safety, but still lacks sufficient supporting data from observational studies or clinical trials.
Abstract #P_13
A two years follow up of 3 HIV children treated with Raltegravir

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Background: The time to achieved HIV Virological suppression in children after starting Antiretroviral treatment (ARV) usually is very long due to high amounts of viral copies. Raltegravir (RAL), has been shown to be effective at controlling HIV viral replication and improving CD4+ count also in HIV infected children but there are still few data in pediatric setting regarding long term drug-related toxicities. We describe three cases of children < 3 years old, treated with RAL evaluating the effectiveness and drug-toxicities in a two year follow-up.

Material and Method: An Antiretroviral (ART) regimen with RAL at age <36 months of age was started in 3 HIV infected children followed for 2 years of follow up. Clinical histories also regarding previous maternal ART therapy were reviewed; prior to starting RAL we evaluated clinical condition and Genotypic resistance test (GRT) results. Laboratory alterations associated with drug-related toxicities was performed every 15 days in the first month after starting RAL treatment and every 1-2 months later on. HIV-1 RNA viral load, CD4+ cells count was performed every 2 months

Results: All three children, 2 male and 1 female were HIV infected for vertical transmission.

All had previously at diagnosis undertaken ARV therapy with a 2 NRTI backbone plus 1 boosted PI or 1 NNRTI or both. In 1 girl (A) treated with ARV from birth, RAL was started at 3 months of age after the results of resistance testing showed the presence of a multi-resistant viral strain (PR: L10I, K20R, M36I, L63T, L89M; RT:M41L, L210W, T215S). In the others 2 boys the HIV/AIDS diagnosis and related Encephalopathy was performed at 8 (B) and 9 (C) months respectively and RAL in addition to ARV treatment was started at 25 months and 36 months respectively, due to a long latency in virological response to ARV. In one of this 2 cases (B) before RAL addition, GRT showed NRTI resistance mutation onset (RT: L74V, Y115F, M184V) which was not present in a previous GRT and that showed a not good adherence.

During 2 years of follow-up the patients showed no drug-related reactions and the drug was well tolerated. In all cases, hepatic values as bilirubin, AST, ALT, GGT was normal. The time to achieved virological suppression was medium 56 w from starting RAL.

Three time points were established, Start of RAL-containing regimen (0) and after 1 year (T1) and after 2 years (T2), the patient’s reviewed parameters were as follows:

A: starting RAL at 3 m of age:
Viral load (copies/ml), 0 - 3.950; T1- 48 ; T2- <40
CD4 (cells/ µl), 0 -2975 T1 -2363; T2 - 1889
The Patient obtained viral suppression after w 49 from start RAL .

B: starting RAL at 25 m. of age
Viral load (copies/ml), 0 - 7200; T1 - 210 ; T2 - <40
CD4 (cells/ µl), 0 - 1657; T1 - 2249 ; T2 - 1529
Patient obtained viral suppression after 96 w from start RAL .

C: starting RAL at 36 m. of age
Viral load (copies/ml), 0 - 32.578; T1 - <40 ; T2 - <40
CD4 (cells/ µl), 0 - 2787; T1 - 1513; T2 - 1282
Patient obtained viral suppression after 24 w from start RAL .

Conclusions: Raltegravir was well tolerated in all patients. After a 2 years of follow up there were no signs of drug-related reactions, no toxicities and achieved virological suppression. Further studies of larger pediatric populations could be performed.
Abstract #P_14
Drug to drug interaction between ART and anti-clotting agents: a case report

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Background: Life expectancy of people living with HIV (PLHIV) has dramatically increased. HIV in older adults presents a number of challenges, especially regarding the management of comorbidities. A multifactorial higher risk of cardiovascular events is recognized, attributable to HIV infection itself, the aging process and the chronic use of some antiretrovirals. Following cardiovascular events, anti-clotting agents sharing the same metabolic pathways of antiretrovirals are often administered. This is the case of clopidogrel, a prodrug that is converted to its active metabolite via cytochromes (CYPs) 3A4, 2B6 and 2C19 and whose co-administration with CYP3A4 inhibitors may lead to inefficacy. This interaction has been well studied with ketoconazole, but little is known about the in vivo interactions with ART.

Material and Methods: In this report we describe the case of a reduced clopidogrel response in an HIV patient administered with Darunavir/Ritonavir 600/100 mg bid, Dolutegravir, Etravirine and Maraviroc.

Case report: A 56 years old Caucasian male, active tobacco smoker was admitted to the Emergency Department (ED) complaining of chest pain and dyspnea. His past medical history included HIV infection since 1991 with a long therapeutic history and many resistance-associated mutations (RAMs), which required the introduction of increasingly complex ART regimens. He also suffered from hypertension (on treatment), type 2 diabetes and had a past history of intravenous drug use. At the ED the patient did not disclose about his HIV status. He was diagnosed with ST-elevation myocardial infarction (STEMI) and was treated with invasive coronary angiography with percutaneous coronary intervention (PCI) and drug-eluting stent (DES). Afterwards, the patient was discharged with the prescription of a dual anti platelet therapy including aspirin and clopidogrel. After one month of treatment, patient was re-admitted to the ED complaining of the same symptoms. Blood tests and electrocardiography revealed a STEMI. The patient underwent invasive coronary angiography, which showed 99% stenosis for intra-stent thrombosis. He was then treated with PCI, stent dilatation and a new DES. The patient then disclosed about his HIV infection and a consultation was required to select the best therapeutic option.

New anticoagulant drugs recommended after cardiac events include ticagrelor, clopidogrel and prasugrel. Co-administration of ticagrelor with inhibitors of CYP3A4 is contraindicated, as it may lead to a substantial increase in its exposure leading to unwanted bleeding events. On the contrary, both clopidogrel and prasugrel are converted to active metabolite by CYP3A4 and its inhibition mainly exerted by ritonavir is likely to decrease their plasmatic concentration. This effect lead to non-responsiveness to clopidogrel and to a reduction in prasugrel active metabolite Cmax and AUC by 45% and 38%, respectively, but without a significant reduction in its efficacy. In this case, in which it was impossible to remove boosted PIs due to patient’s resistance profile, prasugrel was the best choice to treat also his cardiac condition.

Conclusions: We reported this case as an example of drug-drug interaction in HIV subjects with cardiac events, a growing cohort of patients that require a careful assessment by infectious diseases consultants in order to avoid undesired secondary events.
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