Infect Dis Trop Med 2019; 5: e565

Efficacy, safety and tolerability of dolutegravir-based combination antiretroviral therapy in clinical practice in HIV-infected patients: results from a multicenter study

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ABSTRACT:

— ***Objective:*** Dolutegravir (DTG) is a second-generation integrase inhibitor (INI) characterized by unboosted daily dosing, limited cross resistance, and a high barrier to resistance. We aimed to describe the efficacy and safety of DTG-based cART in clinical practice in both naïve and experienced HIV1-infected patients.

— ***Patients and Methods:*** We performed an observational, retrospective, multi-center study. From 2015, all patients starting a new cART regimen containing DTG were enrolled. Clinical and virological details, together with pharmacological history were collected from each patient.

— ***Results:*** Of 210 patients included in the analysis, 157 (74.8%) were males, 185 (87.6%) Caucasians, 43 (20.5%) were co-infected with hepatitis C and 67 (31.9%) had been previously diagnosed as CDC stage C. At baseline, 97 (46.2%) patients had a positive HIV-RNA, of which 43 (20.5%) were ART-naïve subjects. Mean age at enrollment was 47.7±12.2 years, with a median CD4+ count of 453 (IQR 270-693) cells/mm3. Among naïve patients, 34/41 (82.9%) resulted virologically suppressed at 3 months, 23/26 (88.5%) at 6 and 15/17 (88.2%) at 12 months, with an increase in CD4+ count. Among experienced viremic patients, 27/44 (61.4%) resulted virologically suppressed at 3 months, 29/33 (87.9%) and 21/26 (80.8%) respectively at 6 and 12 months, with an increase in CD4+ count. Among experienced patients with suppressed HIV-RNA, 102/109 (93.6%) kept virological suppression at 3 months, 87/93 (93.5%) at 6 and 66/71 (93%) at 12 months. There were only 14 (6.6%) interruptions, 12(5.7%) due to adverse events. There was a significant increase in creatinine levels, whereas no statistically significant changes were observed in lipid or hepatic profile.

— ***Conclusions:*** Our data confirm the high potency of DTG in a HIV-infected naive and experienced patient population. We also evidenced a very rapid CD4 cells increase after only 3 months. Our results also highlight the good tolerability of DTG-based regimens in clinical practice.

— ***Keywords:*** Efficacy, Safety, Dolutegravir, HIV infection, Clinical practice.

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INTRODUCTION

The advent of HAART (highly active antiretroviral therapy) allowed us to switch the medical attention from the acute and opportunistic typical AIDS (acquired immune deficiency syndrome) infections to the "non-AIDS related morbidities", a whole series of long-term complications affecting HIV-infected patients as well as the general population[1,2]. Bone mineral density reduction, kidney disease, non-AIDS defining cancers, neurocognitive disorders, metabolic and cardiovascular disease[3-28]: these are the main issues for long-living HIV-affected patients nowadays, which are mainly age-related but also result to be increased in this kind of patients, due to several years spent on anti-retroviral therapy (ART)[29]. Data from literature showed that the burden of these affections in the long term might be different, based on the type of ART regimen chosen.

Among the latest regimens, the first generation integrase strand-transfer inhibitors (INSTIs) such as elvitegravir and raltegravir already proved to be effective and safe both in naive and experienced HIV-affected patients[30-32], especially showing an excellent tolerability and a very good penetration in the central nervous system[33]. The main flaw for elvitegravir would be the need to be boosted, thus being subjected to a higher number of potential drug-drug interactions; on the other hand, raltegravir may requires a twice-a-daily dosage, reducing the patients' compliance. For these reasons, the advent and the rapidly increased use of the second generation INI dolutegravir (DTG) allowed to further improve combination ART (cART) progresses thanks to its un-boosted daily dosing, a low dosage allowing for fixed-dosed combination, limited cross resistances and a higher barrier to resistance[34-36].

Even though DTG performed very well in clinical trials, showing remarkable efficacy and safety and an outstanding tolerability, there is still a lack of data both on its short and long-term impact in real life[37-41]. For this reason, we aimed to describe the efficacy, safety and tolerability of DTG-based cART in clinical practice in both naïve and experienced HIV-infected patients.

PATIENTS AND METHODS

Patients in the study were enrolled from 4 different centers: Cardiff (University Hospital of Wales, Wales, UK), Sassari (University of Sassari, Sassari, IT), Cagliari (Santissima Trinità Hospital, Cagliari, IT) and Messina (University of Messina, Messina, IT). From 2015, all patients starting a new cART regimen containing DTG were enrolled. No exclusion criteria were applied because the aim was to assess efficacy, safety and tolerability of DTG in real life. Clinical and virological details, together with pharmacological history (ART regimens used in the past), were collected from each patient. Follow-ups were set at 3, 6, and 12 months and all the possible discontinuation causes were recorded. When a discontinuation event was registered due to adverse events, a specific diagnostic algorithm was carried out and the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") was applied with the purpose of evaluating the degree of these reactions.

Statistical analysis

Data in text and tables were reported as descriptive statistics. Student t-test was used to compare continuous variables; χ^2 test or exact Fisher test were performed to compare categorical (qualitative) variables. Paired t-test or Mann Whitney U test were carried out, after having verified the normal distribution, with the purpose of assessing the statistical significance compared to baseline, with statistical significance denoted as $p < 0.05$.

RESULTS

Population characteristics

Since this was a multicenter study, patients were enrolled from different centers: of a total of 210 patients included in the analysis, 120 patients were enrolled in Cardiff, 59 in Sassari, 21 in Messina and 10 patients in Cagliari. Of these 210 patients, 157 (74.8%) were males and 53 (25.2%) females. One hundred and eighty-five (87.6%) were Caucasians, 19 (9%) Africans, 4 (1.9%) Arabians, 2 (1%) Asians and 1 (0.5%) Latin American. Mean age at the moment of the enrollment was 47.7±12.2 years, with a median CD4+ count of 453 (IQR 270-693) cells/mm^3. As regards risk factors for acquiring HIV infection, 71 (33.8%) patients were heterosexuals, 84 (40.1%) homosexuals and 34 (16.2%) patients had a history of drug injection, 4 (1.9%) had a vertical transmission and 1 (0.4%) was infected through blood transfusion; finally, in 16 (7.6%) patients the risk factor remained unknown. In the matter of CDC stage, 59 (28%) patients were in stage A, 84 (40.1%) in stage B and 67 (31.9%) in stage C. At baseline, 113 (53.8%) were virologically suppressed HIV-infected patients and 97 (46.2%) presented certain values of viremia. Of these viremic patients, 43 (44.3%) were ART-naïve subjects. Furthermore, 43 (20.5%) patients were tested HCV positive and 12 (5.7%) HBsAg positive. Among ART-experienced patients, median HAART duration was 84.5 (IQR 48-171) months and 23 (11%) patients had in their history at least one episode of virological failure.

All 210 patients were enrolled in this study because they were either switched to or started with DTG regimen-based ART. They were further divided into three main groups, based on the cART regimen they were submitted to: 1) (Group A) 101 (48.1%) total patients undergone to DTG, abacavir (ABC) and lamivudine (3TC), of whom 28 were treatment-naïve; 2) (Group B) 72 patients (33.8%) with ART regimen based on DTG, tenofovir (TDF) and emtricitabine (FTC), of whom 14 were naïve; 3) (Group C) 37 patients (18.1%) of whom one was naïve, submitted to DTG based ART regimen with other anti-retroviral drugs. Main baseline patients' characteristics have been summarized in Table 1.

Table 1. Main baseline patients' characteristics.

Parameters	Cohort (n=210)
Male Female	157 (74.8%) 53 (25.3%)
Caucasian African	184 (87.6%) 19 (9.0%)
Age (years, mean ± SD)	47.7 ±12.2
CD4 (cells/mm^3, median (IQR))	453 (270-693)
Heterosexual Homosexual	71 (33.8%) 84 (40.1%)
Naive	43 (20.5%)
CDC stage A CDC stage B CDC stage C	59 (28.%) 84 (40.1%) 67 (31.9%)
HCV positive	43 (20.5%)
HBsAg positive	12 (5.7%)
HAART duration (months, median (IQR))	84.5 (48-171)
Previous virological failures	23 (11%)

Efficacy

In order to assess the efficacy of DTG regimen based therapies, viral load and CD4+ count were collected at 3, 6 and 12 months among patients coming from Group A and B and further divided into these three subgroups: Subgroup 1) naïve patients, Subgroup 2) experienced patients with positive viremia at baseline and Subgroup 3) experienced patients who were virologically suppressed at baseline.

Among patients from Subgroup 1, 34/41 (82.9%) resulted virologically suppressed at 3 months, 23/26 (88.5%) at 6 months and 15/17 (88.2%) at 12 months (Figure 1). CD4+ count showed a gradual statistically significant increase compared to baseline at 3 ($p < 0.001$), 6 ($p < 0.001$) and 12 months ($p = 0.004$) (Figure 2).

Among patients from Subgroup 2, 27/44 (61.4%) resulted virologically suppressed at 3 months, 29/33 (87.9%) and 21/26 (80.8%) respectively at 6 and 12 months (Figure 1). All the 7 patients who resulted to still have a positive viremia at 12 months had a viral load under 200 cps/ml, which was supposedly explained to be a viremic blip and not a true virological failure. CD4+ count showed a statistically significant increase compared to baseline both at 3 ($p = 0.007$), 6 ($p = 0.05$), and at 12 months ($p = 0.015$) (Figure 2).

When considering patients from Subgroup 3, 102/109 (93.6%) remained virologically suppressed at 3 months, 87/93 (93.5%) at 6 and 66/71 (93%) at 12 months (Figure 1). All 5 patients with a positive viremia at 12 months showed a viral load under 200 cps/ml. As regards CD4+ count, it showed steady values with no statistically significant differences compared to baseline.

Tolerability

Lipid profile

We assessed the lipid profile in patients with available data, taking into consideration the total cholesterol, HDL cholesterol, HDL/total cholesterol ratio and triglycerides.

When considering naïve patients, 31 of them had available data at baseline, 24 at 3 months, 16 at 6 months and 10 patients at 12 months. During the 12 months follow-up of these patients, total cholesterol values showed a progressive increase. HDL cholesterol showed a rise in the first 6 months and then it inverted the trend at 12 months, showing a decrease. The opposite behavior was showed by triglycerides, progressively decreasing in the first 6 months and then increasing again at 12 months. This apparently weird trend might be explained with the fact that the 10 patients whose lipid profile was evaluated at 12 months had abnormal values already at baseline. Nevertheless, data gathered did not show any statistically significant difference compared to baseline ($p>0.05$).

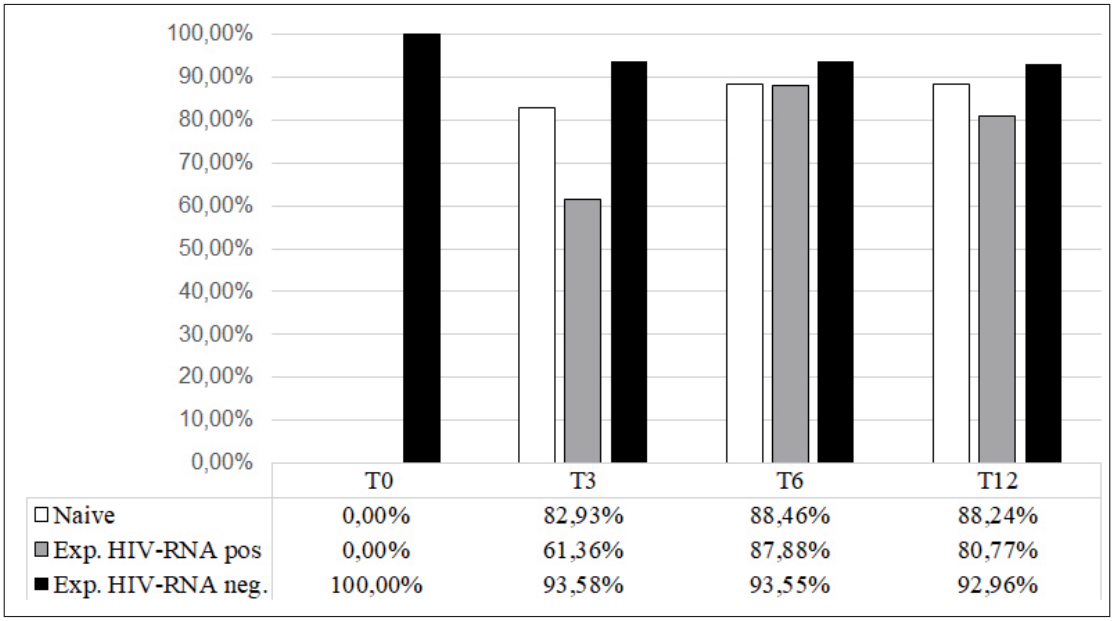

Figure 1.

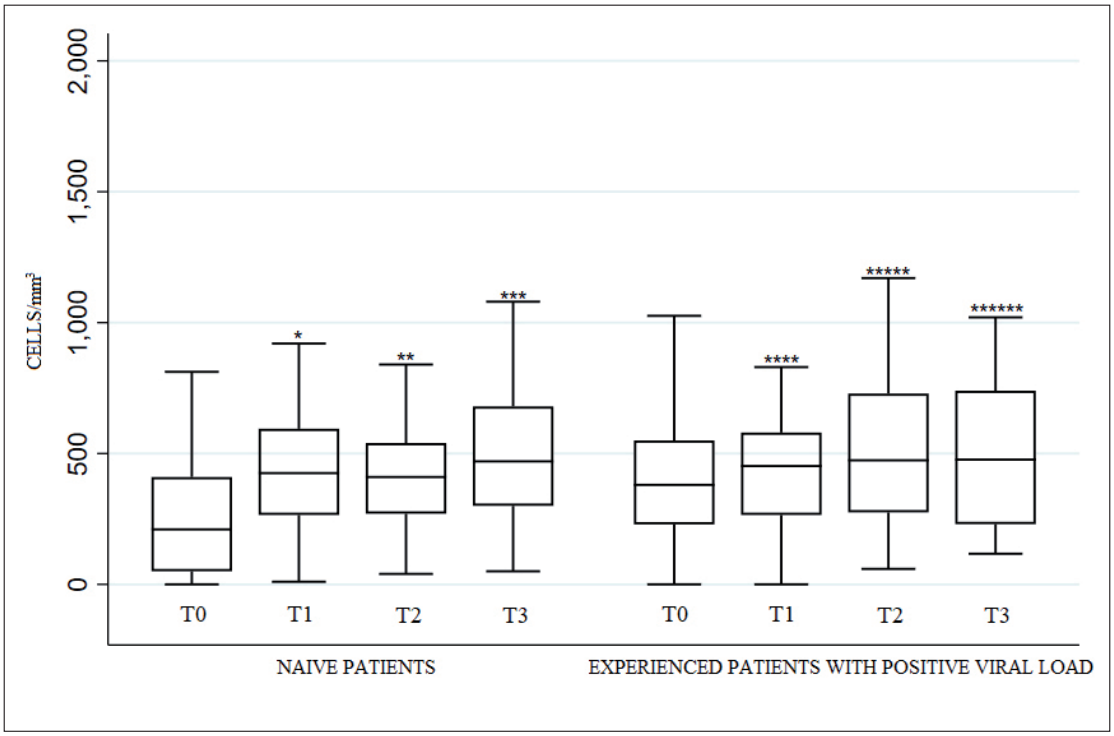

Figure 2.

Concerning experienced patients with suppressed viremia at baseline, 126 of them had available data at baseline, n° 80 at 3 months, n° 60 at 6 months and 55 patients at 12 months. Again, no statistically significant differences were observed in these patients, as well as when stratifying patients on the nucleoside backbone used (ABC/3TC or TDF/FTC).

Hepatic profile

No statistically significant differences were registered when assessing variations in alanine transaminase (ALT), aspartate transaminase (AST), Gamma-glutamyl-transpeptidase (γ-GT) or platelet count.

Renal profile

Serum creatinine values were evaluated for 12 months follow-up, in patients with available data, showing an increasing trend.

In naïve viremic patients, creatinine median value increased from 0.79 mg/dL at baseline to 0.87 mg/dL at 3 and 6 months, up to 0.94 mg/dL at 12 months. In all three cases, changes were statistically significant ($p = 0.005$; $p < 0.001$; $p = 0.014$).

In cART-experienced viremic patients, creatinine median value at baseline was higher (0.85 mg/dL), progressively increasing at 3 (0,88 mg/dL), 6 (0.9 mg/dL) and 12 months (0.93 mg/dL). In these group of patients though, only creatinine values at 3 months resulted statistically significant ($p = 0.001$; $p = 0.1$; $p = 0.15$).

Finally, when taking into consideration all the experienced patients with suppressed viremia at baseline, median creatinine values increased from baseline (0.89 mg/dL) to 3 months follow-up and then it stabilized at 6 and 12 months, with statistically significant values only at 3 and 6 months ($p = 0.02$; $p < 0.001$; $p = 0.12$).

Safety

Among all the 210 enrolled patients, 14 (6.6%) therapy interruptions were registered, one in a naïve and 13 in experienced patients (Figure 3). More in detail, 12 (5.7%) adverse events were seen: 8 (3.8%) affecting the central nervous system (CNS), of which 5 had sleep issues (4 insomnia, 1 vivid dreams and nightmare), 1 case of depression and 2 case of hallucinations (1 visual and 1 auditory). Then, one (0.4%) had gastro-enteric tract problems and 3 (1.4%) for other causes. Finally, one virological failure and one therapy switch during negative viremia were registered in our database.

DISCUSSION

Dolutegravir is widely used in clinical practice for the treatment of HIV infection. Its advantages include the un-boosted daily dosing (which can be taken with or without food), a low dosage allowing for fixed-dosed combination, limited cross resistances and a higher barrier to resistance[36,40,41].

DTG proved a very good *efficacy* in our clinical cohort, obtaining a suppressed viremia in 83% of the naïve patients at only 3 months and 88% after 12 months of treatment. Great efficacy was showed even in experienced and naïve highly viremic patients, in which almost 88% of patients reached an undetectable viral load after 6 months

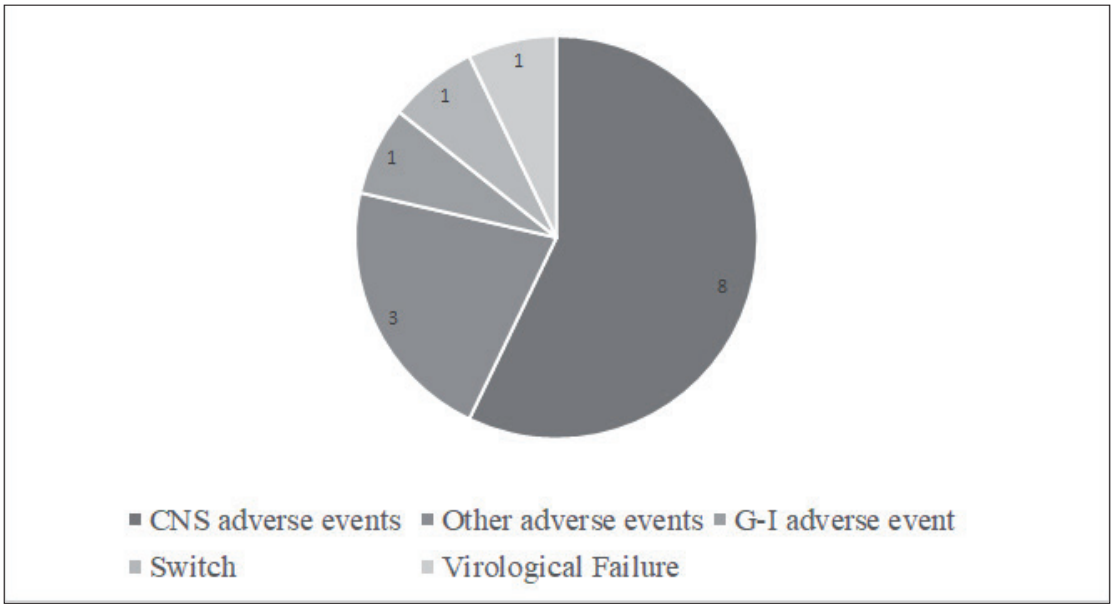

Figure 3.

of treatment. In this group, the proportion of patients with sustained virological efficacy at 12 months decreased to 80%, but that might be explained with the fact that all the 7 patients who were still viremic at 12 months resulted having a viral lower than 200 cps/ml, fitting with viremic blips more that with virological failures. All these results proved the power of DTG based cART regimens even in pretreated and previously failed patients, showing its ability to be effective in complicate patients as well. As regards CD4+ count, DTG proved its efficacy in both naïve and experienced patients, showing an increase in CD4+ in viremic patients and stable CD4+ count when looking at experienced patients with suppressed viremia.

Safety of DTG was also demonstrated in this real-life study, with only 14 (6.6%) interruptions, 12 (5.7%) due to adverse events.

On the subject of *tolerability*, a statistically significant increase in creatinine levels has been shown. This event was explicable with the inhibiting action of DTG on the creatinine transporter OCT2 situated in the proximal tubule of the nephron, causing a decrease in creatinine excretion and its rise in plasmatic levels. Lipid profile in patients undergoing DTG showed a slight increase in cholesterol and triglycerides when looking at naïve patients and, on the other hand, a general improvement (decrease in cholesterol and triglycerides, increase in HDL and ratio) in experienced patients. Even if these events resulted positive in their trend and in line with previous data from literature clinical trials, our results did not show any statistically significance, may be due to the scarce number of patients enrolled in this study. Finally, DTG hepatic safety was confirmed, showing no significant adverse events in our patients.

CONCLUSIONS

Our data strengthened the results from DTG clinical trials, confirming DTG-based cART high potency and effectiveness in both naïve and experienced patients the in real life.

Conflict of Interests:
GM has received advisory board and/or speaking fees from Gilead Sciences, ViiV, Merck, Sharp and Dohme, Janssen; AF has received fees for attending advisory boards from both ViiV and Gilead and funding to attend scientific conferences from Merck, Sharp and Dohme.

REFERENCES

1. Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ 2009; 338: a3172-a3172.
2. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet 2013; 382: 1525-1533.
3. Bonfanti P, Ricci E, de Socio G, Zeme D, Carradori S, Penco G, Parruti G, Grosso C, Madeddu G, Vichi F, Bini T, Martinelli C, Melzi S, Quirino T, CISAI Study Group. Metabolic syndrome: a real threat for HIV-positive patients?: Results from the SIMONE study. J Acquir Immune Defic Syndr 2006; 42: 128-131.
4. Bonfanti P, De Socio G, Marconi P, Franzetti M, Martinelli C, Vichi F, Penco G, Madeddu G, Orofino G, Valsecchi L, Vitiello P, Menzaghi B, Magni C, Ricci E. Is Metabolic Syndrome Associated to HIV Infection Per Se? Results from the HERMES Study. Curr HIV Res 2010; 8: 165-171.
5. Simonelli C, Tedeschi R, Gloghini A, Talamini R, Bortolin MT, Berretta M, Spina M, Morassut S, Vaccher E, De Paoli P, Carbone A, Tirelli U. Plasma HHV-8 viral load in HHV-8-related lymphoproliferative disorders associated with HIV infection. J Med Virol 2009; 81: 888-896.
6. Berretta M, Garlassi E, Cacopardo B, Cappellani A, Guaraldi G, Cocchi S, De Paoli P, Lleshi A, Izzi I, Torresin A, Di Gangi P, Pietrangelo A, Ferrari M, Bearz A, Berretta S, Nasti G, Di Benedetto F, Balestreri L, Tirelli U, Ventura P. Hepatocellular carcinoma in HIV-infected patients: check early, treat hard. Oncologist 2011; 16: 1258-1269.
7. Berretta M, Zanet E, Basile F, Ridolfo AL, Di Benedetto F, Bearz A, Berretta S, Nasti G, Tirelli U. HIV-positive patients with liver metastases from colorectal cancer deserve the same therapeutic approach as the general population. Onkologie 2010; 33: 203-204.

8. Berretta M, Lleshi A, Cappellani A, Bearz A, Spina M, Talamini R, Cacopardo B, Nunnari G, Montesarchio V, Izzi I, Lanzafame M, Nasti G, Basile F, Berretta S, Fisichella R, Schiantarelli C C, Garlassi E, Ridolfo A, Guella L, Tirelli U. Oxaliplatin based chemotherapy and concomitant highly active antiretroviral therapy in the treatment of 24 patients with colorectal cancer and HIV infection. Curr HIV Res 2010; 8: 218-222.
9. Scarpino M, Pinzone MR, Di Rosa M, Madeddu G, Focà E, Martellotta F, Schioppa O, Ceccarelli G, Celesia BM, d'Ettorre G, Vullo V, Berretta S, Cacopardo B, Nunnari G. Kidney disease in HIV-infected patients. Eur Rev Med Pharmacol Sci 2013; 17: 2660-2667.
10. Castronuovo D, Cacopardo B, Pinzone MR, Di Rosa M, Martellotta F, Schioppa O, Moreno S, Nunnari G. Bone disease in the setting of HIV infection: update and review of the literature. Eur Rev Med Pharmacol Sci 2013; 17: 2413-2419.
11. Madeddu G, Spanu A, Solinas P, Calia GM, Lovigu C, Chessa F, Mannazzu M, Falchi A, Mura MS, Madeddu G. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. Q J Nucl Med Mol Imaging 2004; 48: 39-48.
12. Madeddu G, Spanu A, Solinas P, Babudieri S, Calia GM, Lovigu C, Mannazzu M, Nuvoli S, Piras B, Bagella P, Mura MS, Madeddu G. Different impact of NNRTI and PI-including HAART on bone mineral density loss in HIV-infected patients. Eur Rev Med Pharmacol Sci 2015; 19: 4576-4589.
13. Zanet E, Berretta M, Benedetto F Di, Talamini R, Ballarin R, Nunnari G, Berretta S, Ridolfo A, Lleshi A, Zanghì A, Cappellani A, Tirelli U. Pancreatic cancer in HIV-positive patients: a clinical case-control study. Pancreas 2012; 41: 1331-1335.
14. Pinzone MR, Di Rosa M, Cacopardo B, Nunnari G. HIV RNA suppression and immune restoration: can we do better? Clin Dev Immunol 2012; 2012: 515962.
15. De Socio GVL, Ricci E, Parruti G, Maggi P, Madeddu G, Quirino T, Bonfanti P. Chronological and biological age in HIV infection. J Infect 2010; 61: 428-430
16. Pinzone MR, Di Rosa M, Malaguarnera M, Madeddu G, Focà E, Ceccarelli G, D'Ettorre G, Vullo V, Fisichella R, Cacopardo B, Nunnari G. Vitamin D deficiency in HIV infection: An underestimated and undertreated epidemic. Eur Rev Med Pharmacol Sci 2013; 17: 1218-1232.
17. Fontana Del Vecchio R, Pinzone M, Cacopardo B, Nunnari G. Anal cancer in HIV-positive patients. World Cancer Res J 2014; 1: e405-411.
18. Carbone A, Gloghini A, Vaccher E, De Paoli P. Lymphomas and other cancers in HIV-infected patients. World Cancer Res J 2014; 1: e291-295.
19. Di Francia R, Fierro C, Di Paolo M, Siesto S, Cacopardo B, Cilenti L, Atripaldi L. Selected pharmacogenetic panel test for toxicity prevention of drug-drug interactions between highly active antiretroviral therapy (HAART) and antiblastic chemotherapy. World Cancer Res J 2015; 2: e492-502.
20. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, Collier AC, Gelman B, McArthur J, Morgello S, McCutchan JA, Grant I. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS 2011; 25: 1747-1751.
21. Lai V, Fiore V, Calia GM, Lovigu C, Zizzi B, Budroni C, Peruzzu F, Bagella P, Mura MS. Relationship between neurocognitive impairment and cardiovascular risk in an HIV-infected patient: a case report. Infect Dis Trop Med 2015; 1: e182-184.
22. Bonfanti P, De Socio GV, Ricci E, Antinori A, Martinelli C, Vichi F, Penco G, Madeddu G, Orofino G, Valsecchi L, Rusconi S, Menzaghi B, Pocaterra D, Quirino T. The feature of Metabolic Syndrome in HIV naive patients is not the same of those treated: results from a prospective study. Biomed Pharmacother 2012; 66: 348-353.
23. Madeddu G, Fois AG, Calia GM, Babudieri S, Soddu V, Becciu F, Fiori ML, Spada V, Lovigu C, Mannazzu M, Caddeo A, Piras B, Pirina P, Mura MS. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? Infection 2013; 41: 347-353.
24. Schillaci G, Maggi P, Madeddu G, Pucci G, Mazzotta E, Penco G, Orofino G, Menzaghi B, Rusconi S, Carenzi L, Celesia BM, Martinelli C, Bonfanti P, De Socio GV, CISAI Study Group. Symmetric ambulatory arterial stiffness index and 24-h pulse pressure in HIV infection: results of a nationwide cross-sectional study. J Hypertens 2013; 31: 560-567.
25. Zanet E, Berretta M, Martellotta F, Cacopardo B, Fisichella R, Tavio M, Berretta S, Tirelli U. Anal cancer: Focus on HIV-positive patients in the HAART-era. Curr HIV Res 2011; 9: 70-81.
26. Pinzone MR, Fiorica F, Di Rosa M, Malaguarnera G, Malaguarnera L. Non-AIDS-defining cancers among HIV-infected people. Eur Rev Med Pharmacol Sci 2012; 16: 1377-1388.
27. Berretta M, Cinelli R, Martellotta F, Spina M, Vaccher E, Tirelli U. Therapeutic approaches to AIDS-related malignancies. Oncogene 2003; 22: 6646-6659.
28. Berretta M, Cappellani A, Di Benedetto F, Lleshi A, Talamini R, Canzonieri V, Zanet E, Bearz A, Nasti G, Lacchin T, Berretta S, Fisichella R, Balestreri L, Torresin A, Izzi I, Ortolanik P, Tirellia U. Clinical presentation and outcome of colorectal cancer in HIV-positive patients: A clinical case-control study. Onkologie 2009; 32: 319-324.
29. Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD; DAD study group. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS 2003; 17: 1179-1193.
30. Wohl D, Gallant JE, Zhong L, Yale KB, White K, Kearney Pharm D BP, Szwarcberg J, Quirk E, Cheng AK, Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, Gallant JE, Liu HC, Zhong L, Yale K, White K, Kearney BP, Szwarcberg J, Quirk E, Cheng AK. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012; 379: 2439-2448.
31. Molina JM, Lamarca A, Andrade-Villanueva J, Clotet B, Clumeck N, Liu YP, Zhong L, Margot N, Cheng AK, Chuck SL; Study 145 Team. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. Lancet Infect Dis 2012; 12: 27-35.
32. Lennox JL, Dejesus E, Berger DS, Lazzarin A, Pollard RB, Valdez J, Madruga R, Zhao J, Wan H, Gilbert CL, Teppler H, Rodgers AJ, Barnard RJO, Miller MD, Dinubile MJ, Nguyen B-Y, Leavitt R, Sklar P. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr 2010; 55: 39-48.
33. Podany AT, Scarsi KK, Fletcher CV. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors. Clin Pharmacokinet 2017; 56: 25-40.
34. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, Baril J-G, Domingo P, Brennan C, Almond S, Min S. Articles Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013; 13: 927-935.

35. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, Pokrovskiy V, Fehr J, Ortiz R, Saag M, Harris J, Brennan C, Fujiwara T, Min S; ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1infection (FLAMINGO): 48 week results from the randomised open-label phase 3 b study. Lancet 2014; 383: 2222-2231.
36. Raffi F, Rachlis A, Brinson C, Arasteh K, Gó Rgolas M, Brennan C, Pappa K, Almond S, Granier C, Nichols WG, Cuffe RL, Eron J, Walmsley S. Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naive HIV-infected individuals in three randomized trials. AIDS 2015; 29: 167-174.
37. Quercia R, Roberts J, Louise MC, Zala C. Comparative Changes of Lipid Levels in Treatment-Naive, HIV-1-Infected Adults Treated with Dolutegravir vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Darunavir-Based Regimens Over 48 Weeks. Clin Drug Investig 2015; 35: 211-219.
38. De Boer MGJ, Van Den Berk GEL, Van Holten N, Oryszcyn JE, Dorama W, Ait Moha D, Brinkman K, To C. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS 2016; 30: 2831-2834.
39. Capetti AF, Sterrantino G, Cossu MV, Orofino G, Barbarini G, De Socio GV, Di Giambenedetto S, Di Biagio A, Celesia BM, Argenteri B, Rizzardini G. Switch to Dolutegravir plus Rilpivirine Dual Therapy in cART-Experienced Subjects: An Observational Cohort. PLoS One 2016; 11: e0164753.
40. Clotet B, Feinberg J, Lunzen J, Khuong-Josses M-A, Antinori A, Dumitru Ei, Pokrovskiy V, Fehr J, Ortiz R, Saag M, Harris J, Brennan C, Fujiwara T, Min S. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014; 383: 2222-2231.
41. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, Bloch M, Podzamczer D, Pokrovsky V, Pulido F, Almond S, Margolis D, Brennan C, Min S; SPRING-2 Study Group. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013; 381: 735-743.