European Review for Medical and Pharmacological Sciences 2023; 27: 4185-4201

New treatment strategies for HIV-positive cancer patients undergoing anticancer medical treatment: update of the literature

M. BERRETTA[1], B.A. FACCHINI[2], A. COLPANI[3], R. DI FRANCIA[4], M. MONTOPOLI[5,6], G. PELLICANÒ[7], U. TIRELLI[8], F. FIORICA[9], A. OTTAIANO[10], G. MADEDDU[3], A. DE VITO[3]

[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[2]Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[3]Department of Medicine, Unit of Infectious Disease, Surgery and Pharmacy, University of Sassari, Sassari, Italy
[4]IAPharmagen, Italian Association of Pharmacogenomics and Molecular Diagnostics, Ancona, Italy
[5]Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy
[6]Veneto Institute of Molecular Medicine, University of Padua, Padua, Italy
[7]Department of Human Pathology of the Adult and the Developmental Age "G. Barresi", University of Messina, Messina, Italy
[8]Tirelli Medical Center, Pordenone, Italy
[9]Department of Oncology, Legnago, Verona, Italy
[10]Istituto Nazionale Tumori di Napoli, IRCCS "G. Pascale", Naples, Italy

M. Berretta and B.A. Facchini are co-first authors

Abstract. – The introduction of highly active antiretroviral therapy (ART) has deeply modified the outcome of HIV patients by improving their overall survival and ameliorating their quality of life (QoL). The prolongation of these patients' survival has led to an increased risk of highly diffused non-infectious diseases, e.g., cardiovascular diseases, endocrine disease, neurological diseases, and cancer.

The management of antiretroviral therapy and anticancer agents (AC) can be challenging, due to the possible drug-drug interactions (DDI) between AC and ART. For this reason, a multidisciplinary approach is always preferred as demonstrated by the GICAT (Italian Cooperation Group on AIDS and Tumors). This review aims to analyze the current scientific data regarding the possible effects of ART on the management of HIV-positive cancer patients and to evaluate the possible DDIs that must be taken into consideration when co-administrating ART and AC. A collaboration between all the involved professional figures, particularly infectious disease specialists and oncologists, represents the key to the correct managing of these patients in order to guarantee the best oncological outcome possible.

Key Words:
Drug metabolism, Pharmacogenomics, Pharmacogenetics, Cytochrome P450, Cancer, AIDS, Individualized therapy.

Introduction

The introduction of highly active antiretroviral therapy (ART) has deeply modified the outcome of HIV patients by improving their overall survival. Furthermore, the increase in life expectancy has led to an amplified risk of non-AIDS-related morbidity including cardiovascular diseases, neurological diseases, metabolic dysfunctions, and cancer[1,2]. The GICAT (Italian Cooperation Group on AIDS and Tumors) has demonstrated that a multidisciplinary approach in this particular setting of patients is the best way to obtain good and safe results. Patients who receive a combination of anticancer agents (AC) and ART can achieve better responses and survival rates than patients who receive AC alone. However, careful attention must be paid to cross toxicity and possible pharmacokinetic and pharmacodynamic interactions between antiretroviral drugs and AC.

Methods

To assess the current state of ART for the treatment of HIV in cancer patients, a search of the Cochrane Library and PubMed was performed by

Corresponding Author: Massimiliano Berretta, MD, Ph.D; e-mail: berrettama@gmail.com

crossing the key words "antiretroviral therapy" AND "cancer therapy" AND "HIV" limited to the English literature but with no time restriction. The titles of the 1,753 papers retrieved have been examined.

Papers that included only case reports were excluded. Ambiguous titles were primarily included, leaving 240 articles. For studies conducted by the same research institute at different times, the most recent and complete study was included, unless different methods or endpoints or specific issues had been addressed. Papers whose full text or at least abstract were not available were excluded, in addition to 698 free articles. Ultimately, 123 reviews (all free articles) and 75 clinical trials were retrieved, fulfilling the requirements for analysis.

HIV and Cancer

Among the cancers described in HIV patients, it is possible to distinguish AIDS-defining cancers (ADCs), such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, and non-AIDS defining cancers (NADCs), including hepatocellular carcinoma (HCC), anal cancer, lung cancer, colorectal cancer (CRC), gastrointestinal cancer (GI), breast cancer and Hodgkin's lymphoma (HL)[3-9].

As a consequence of the advent of ART and improved immune function, the incidence of ADCs has significantly declined[6]. On the other hand, NADCs have gradually emerged as a major fraction of the overall cancer burden[3]. It is well known that cancer risk is higher in people living with HIV (PLWH) compared to the universal population, partly due to the high occurrence of cancer risk factors, such as smoking, alcohol consumption, human papilloma virus (HPV) and EBV, HBV or HCV infection among HIV-infected individuals[10,11]. Longer duration of HIV infection and a history of repeated opportunistic infections are also considered relevant risk factors for NADCs. Data about the role of immunosuppression in the development of NADCs are controversial. Patel et al[11] found an increased risk of developing CRC in the presence of a low nadir CD4 cell count, while in other papers, no association between the degree of immunosuppression and the development of NADCs has been described[11-13].

In PLWH, cancer represents the first cause of death. Records in the literature have shown that in PLWH, NADCs are usually characterized by a higher grade, more aggressive clinical course, more rapid progression, advanced stages at cancer diagnosis and shorter survival compared with HIV-negative (HIV-) individuals[5,14,15].

Prevention is fundamental to lower the risk of NADCs in PLWH. To reduce lung and oral cavity cancer quitting smoking is highly suggested. Considering that most of liver cancers in PLWH are related to HBV or HCV infections, undergoing periodical hepatitis screening tests could lead to a precocious antiviral treatment and consequently to a reduction in HCC incidence[16,17]. Anal pap-test, high resolution anoscopy and periodical digital anal examination should be taken into consideration in PLWH with high risk of anal cancer for a precocious diagnosis of anal cancer or pre-malignant lesions[18].

Anal Cancer

Anal squamous cell carcinoma (ASCC) is an infrequent neoplasia in the overall population[19-21]. Two meta-analyses[22,23] recognized a 30-fold increased risk for anal cancer among HIV+ people in comparison with the general population. Due to the role of high-risk types of human papillomavirus (hr-HPV), especially HPV-16, and sexual transmission of HPV through anal intercourse, the risk is particularly higher in HIV-infected men who have sex with men[19]. HIV infection is likely to facilitate persistence of HPV infection in the anal region and increase the risk of anal squamous intraepithelial lesions[24]. In a retrospective study[25], a predominance of advanced disease at the time of diagnosis in PLWH was observed compared to the general population, where ASCC is predominantly a loco-regional disease and rarely metastatic at the time of diagnosis. This evidence is probably a result of the effect of HIV infection and immune suppression on the natural history of anal HPV infection[25,26]. Therefore, ART could possibly have an impact on the reduction of invasive forms of ASCC in HIV+ patients[27]. Notably, before the introduction of ART, HIV+ patients with ASCC treated with chemotherapy had a poorer outcome than the general population. Many studies[1,7,28] have demonstrated a poorer therapy tolerability in HIV-infected patients with ASCC compared with the general population due to unforeseeable interactions of chemotherapy with ART. In fact, protease inhibitors and non-nucleoside reverse transcriptase inhibitors are substrates and potent inhibitors or inducers of the cytochrome P450

(CYP) system. The co-administration of anti-neoplastic drugs and ART could result in either drug accumulation and possible toxicity or decreased efficacy of one or both classes of drugs[28].

In the ART era, the 5-year overall survival of HIV+ patients with ASCC has improved and is reported to be similar to the general population. These data may be explained by the fact that patients with ASCC are treated with standard treatments plus ART with good efficacy and acceptable toxicity. This result is possible through the use of the best treatment modalities according to disease stage. According to the Italian guidelines[29], standard treatments for localized and locally advanced disease are different if we consider the anal margin and the anal canal tumors. In the anal margin tumors, the standard treatment for the localized, well-differentiated forms (stage I, G1) consists of local excision alone; more extended or less differentiated tumors (stage I G2-3, Stage II-III), instead, have chemoradiotherapy based on Mitomycin C and 5-Fluorouracile as their primary treatment that has, over time, taken over the previously used aggressive surgical interventions. On the other hand, anal canal tumors are treated with radiotherapy alone or in association with chemotherapy in stage I, chemoradiotherapy with Mitomycin C and 5-Fluorouracile for stage II-III. Standard treatment in stage IV disease (for both anal margin and canal) consists of systemic chemotherapy with Cisplatin + 5-Fluorouracil or Carboplatin + Paclitaxel regimens. During the past years a new treatment has been taking place after the failure of one or more lines of conventional chemotherapy, represented by immunotherapy[30]. In particular, anti PD-1 antibodies do not represent a standard treatment in Italy yet, but they are likely to become it in the near future.

Lung Cancer

Lung cancer represents the most recurrent NADC in HIV+ people[3]. Numerous reports[12,13,31] have shown augmented rates of lung cancer in HIV-infected patients compared with uninfected patients. In a recent meta-analysis[31] of seven studies considering 44,172 people with HIV/AIDS globally, of whom 1,297 were diagnosed with lung cancer, Grulich et al[31] estimated an overall HIV-associated lung cancer risk of 2.7 (95% CI 1.9-3.9). Analogously, the risk for lung cancer related to HIV infection was estimated to be increased 2.6-fold (95% CI 2.1-3.1) in another meta-analysis by Shiels et al[32]. The increased incidence of lung cancer may be related to different factors, such as the prolonged life expectancy of HIV+ patients during the ART era, the longer period of immune suppression status of these patients and the high number of cigarettes they smoke[33]. In fact, among HIV+ individuals, smoking rates range from 35% to 70% compared to approximately 20% in the general US population[34,35]. The introduction of ART has not significantly modified the risk of lung cancer in the setting of HIV infection. Engels et al[12] reported that the relative risk (RR) of lung cancer occurring during the pre-ART era was like that described in the early and recent ART era. In a recent report by Berretta et al[36], data on the impact of ART on the natural history of lung cancer in PLWH were reported, comparing patients with HIV-lung cancer treated in the pre-ART era *vs.* the ART era. This report clearly shows that the improvement in clinical conditions, which were experienced after ART became available, led to a more extensive treatment of lung cancer in these patients and to better outcomes. In fact, chemotherapy was much more frequent among post-ART patients, of whom 27 were treated (79.4%) *vs.* 16 (48%) in the pre-ART group, p=0.04. In the authors' opinion, this may be due to the improved clinical features of patients at the time of diagnosis, the results of the 1995 meta-analysis[13] and a growing number of papers[1,7,28] confirming that the association between chemotherapy and antiretroviral therapy is feasible and safe. For this reason, they strongly advise that patients with advanced lung cancer and HIV are treated in accordance with the standard policy for HIV- patients[36-40]. Surgery still represents the gold standard treatment in the localized disease (stage I, II, resectable stage III), potentially followed by platinum-based combination adjuvant chemotherapy for stage II-III. Locally advanced disease (unresectable stage III) finds in chemoradiotherapy the primary treatment, followed by consolidation immunotherapy with Durvalumab for 12 months in tumors with PD-L1 expression over 1%. Advanced disease should be divided in two subgroups: oncogene addicted and non-oncogene addicted tumors. In the former, treatment is based on TKi directed against the driver oncogene mutation of the neoplastic cells (for example: Osimertinib in EGFR-mutated tumors, Alektinib in ALK rearranged tumors, etc.). The latter, on the other hand, is treated with Pembrolizumab alone if PD-L1 expression in neoplastic cells is over 50%; otherwise, combination of Platinum,

Pemetrexed and Pembrolizumab for non-squamous histology or Platinum, Paclitaxel and Pembrolizumab for squamous histology represent the gold standard (after four cycles, if stable disease or objective response, a maintenance treatment with Pemetrexed + Pembrolizumab and Pembrolizumab single agent respectively must be taken into consideration). Recently, a new combination of two immunotherapeutic agents associated with standard chemotherapy has been approved as first line treatment, based on Checkmate-9LA trial: Carboplatin + Pemetrexed + Nivolumab + Ipilimumab for non-squamous histology and Carboplatin + Paclitaxel + Nivolumab + Ipilimumab for squamous histology. Treatments after first line should be based on non- cross-reactive drugs: immunotherapy with Nivolumab, Pembrolizumab or Atezolizumab if no immunotherapeutic agent has been previously used; Docetaxel (in combination with Nintedanib in non-squamous histology) in every other case[41].

Colorectal Cancer

Colorectal cancer (CRC) is the second most frequent cause of cancer death in Western countries[42]. As for other NADCs, CRC is usually characterized by a higher grade, more aggressive clinical course, more rapid progression, advanced stage, and shorter survival compared with HIV-negative individuals[5,14]. Data on the incidence and natural history of CRC in HIV-infected people are limited. Patel et al[11] reported an increased incidence of CRC in the HIV setting. This evidence probably depends on the longer life expectancy of HIV+ patients due to ART application in clinical practice. On the other hand, large reviews of matched cancer and AIDS registries do not show the same results, probably because PLWH were less likely to undergo any CRC screening examination (flexible sigmoidoscopy, fecal occult blood test, air contrast barium enema) than uninfected subjects[43-46]. In a GICAT report, PLWH had a poorer PS, an unfavorable Dukes' stage, a higher grading, and shorter survival than uninfected subjects[47]. Moreover, they demonstrated that the concomitant use of chemotherapy and ART is safe and feasible and that the efficacy and results are similar to those obtained in the general population, especially when a multidisciplinary approach is adopted[48-53]. Considering that CRC is especially amenable to screening, as premalignant adenomas exhibit a slow progression to malignancy and are often visibly identifiable and treatable *via* colonoscopy, future research should specifically address the issue of screening for HIV-infected subjects to determine the appropriate age to start screening, the frequency of screening and the most cost-effective screening technique for this subgroup of subjects[36]. In the localized and locally advanced colon cancer the gold standard is still represented by surgery, followed by adjuvant chemotherapy in selected cases (stage II with risk factors, stage III). Systemic therapy represents the only possible weapon in the palliative setting: doublets based on 5-Fluorouracil (or Capecitabine) associated with Oxaliplatin or Irinotecan or triplets based on all the aforementioned drugs in selected cases, always associated with anti-EGFR or anti-VEGF drugs depending on K-Ras, N-Ras, and B-RAF status, represent the standard of care. Immunotherapy has become a fundamental weapon even in colorectal cancer: Pembrolizumab is the standard of care in patients with advanced colorectal cancer and MSI-H status. Brilliant results have been registered in trials (NCCN-guidelines)[54] even in the neoadjuvant setting, even though it is not worldwide used in clinical practice yet.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and according to the World Health Organization report, the fourth most common cause of death[43]. The risk for HCC is seven-fold higher in PLWH than in the general population[55,56]. Since the introduction of ART, no incidence of HCC has been observed, unlike other HIV-associated cancers. In HIV patients co-infected with HCV or HBV, the risk of developing HCC is common and significantly higher as a result of chronic viral hepatitis. Little is known about the interactions between HIV and HBV and/or HCV over the long term, although some studies[36,43] have suggested that HIV co-infection seems to accelerate disease progression and reduce the efficacy of anti-HCV and anti-HBV therapies. In addition to potential indirect effects of HCC risk through improvements in immune reconstitution and survival, ART is known to have some direct hepatotoxic effects, especially among PLWH chronically infected with HBV or HCV[57]. In a recent case series[57], the authors reported that PLWH are significantly younger than uninfected patients at HCC diagnosis and were co-infected with HBC or HCV in most

cases. The CD4 cell count at diagnosis was not independently associated with survival; patients receiving ART with undetectable HIV RNA at diagnosis had a better prognosis than untreated subjects or subjects with higher HIV viral load[56-58]. Regarding the therapeutic approach, a GICAT report demonstrated that both curative and palliative therapies are feasible and safe[59-65]. In conclusion, prevention and early diagnosis are key points for the management of HCC, but at present, there are no universal guidelines, especially in PLWH[56]. As for the general population, primary prevention should consist of promoting alcohol avoidance and HBV vaccination, while secondary prevention should be based on the use of ultrasonography and alpha-fetoprotein measurements every six months. Treatments vary depending on tumor extension and liver function (defined using Child-Pugh classification). For the localized disease hepatic resection, liver transplantation, thermoablation or TACE represent the alternatives to consider. In particular, many studies[66-68] have been conducted regarding liver transplantation in PLWH with HCC, showing encouraging results. In the palliative treatment setting, the association of Atezolizumab + Bevacizumab represents the standard of care; Sorafenib or Lenvatinib can be used as alternatives. Due to the recent approval of the immunotherapeutic and antiangiogenetic combination there is still much to understand about its possible interaction with ART in HIV positive patients. The efficacy and safety of the concomitant use of sorafenib and ART are similar to those of the general population[65].

Hodgkin's Lymphoma

HIV-associated Hodgkin's lymphoma (HIV-HL) displays some specific characteristics when compared with HL in the general population[69,70]. First, before ART availability, HIV-HL showed an unusually aggressive clinical behavior and was associated with a poor prognosis. Second, the pathologic spectrum of HIV-HL differs markedly from the general population, with a predominance of unfavorable histological subtypes such as the mixed cellularity (MC) subtype[71,72]. HIV-infected persons have a 10-fold higher risk of developing HL than HIV-negative persons of the same age and gender. In particular, this risk is greater in HIV-infected individuals with moderate immune suppression[73]. A potential explanation is linked to the role of RS cells, which are able to produce several growth factors that increase the influx of CD4 cells and inflammatory cells, which, in turn, provide proliferation signals for RS neoplastic cells. In the case of severe immune suppression leading to an unfavorable milieu, the progression of the RS neoplastic cells may be compromised[74-76]. In addition, HIV-HL is EBV associated in approximately 90% of cases, in contrast to what is observed in the general population, where this association is only observed in 20-50%, probably because the simultaneous or sequential activation of signaling pathways involved in the promotion of cell activation, growth, and survival contributes to most of the features of HIV-HL[72,77]. As for HIV-NHL, one of the most peculiar features of HIV-HL is the frequency of systemic B symptoms and the widespread extent of the disease at presentation, with frequent involvement of extra-nodal sites, particularly bone marrow (23-50%), liver (10-40%), and spleen (20-25%)[65,78-80]. The widespread use of ART has resulted in a substantial improvement in the survival of patients with HIV infection and HL due to the reduction of the occurrence of opportunistic infections and in the opportunity to allow more aggressive chemotherapy[81-86]. In a GICAT report[36], unlike patients who never experienced ART, patients in ART before the onset of HL were older and had less B symptoms, in addition to a higher leukocyte and neutrophil count and hemoglobin levels. A better overall survival (OS) was associated with MC subtype, the absence of extra nodal involvement, the absence of B symptoms, and prior use of ART. Interestingly, three parameters were associated with a better time to treatment failure: a normal value of alkaline phosphates, prior exposure to ART, and an international prognostic score (IPS)<3[87]. In similar studies[87,88], no differences were found between groups at baseline, but complete remission (CR) and overall survival rates were significantly higher in the ART groups. Regarding treatment, results from recent studies[89,90] provide some evidence of the optimal treatment approaches for HIV-HL. Because most patients have advanced stage disease, combination chemotherapy regimens should usually be administered. In summary, the outcome of patients with HIV-HL has improved thanks to the combination of antineoplastic and antiretroviral approaches. The majority of the chemotherapy regimens used in the general population have been tested in PLWH: being ABVD the less toxic it should be preferred, reducing bleomycin to only 2 cycles in patients with compromised lung capacity[91]. The main im-

portant challenges for the coming years are (a) to validate the role of PET scanning both in the staging and in response evaluation, (b) to better understand the interactions between chemotherapy and antiretroviral therapy to reduce the toxicity of both approaches, (c) to evaluate the use of new drugs (i.e., brentuximab vedotin) in this setting, and (d) to evaluate the long-term toxicity of the treatment in cured patients[36].

Anticancer Agents and Art

Patients who receive a combination of anticancer agents (AC) and ART can achieve better response and survival rates than patients who receive AC only. However, careful attention must be paid to cross toxicity and possible pharmacokinetic and pharmacodynamic interactions between antiretrovirals and AC. In general, drug-drug interactions (DDIs) occur when one drug influences the level or activity of another when concurrently administered. They may result in increased therapeutic or adverse effects, decreased therapeutic or adverse effects or a unique response that does not occur when either agent is administered alone[92]. This may be due to the narrow therapeutic index and the inherent toxicity of anticancer agents. In most cases, the consequences of DDIs compromise the efficacy of therapeutic agents or enhance their toxicity. In this field, data on DDIs in the treatment of HIV-associated malignancies are scarce[93]. Few examples show a correlation between toxicities and single nucleotide polymorphisms (SNPs) in the genes coding for metabolizing enzymes and drug transporters. Recently, long-acting antiretroviral therapy holds the promise of new options for treatment. Their conditions where long-acting schedules have proven cost-effectivenesses, such as contraception and mental health, are of particular interest. Long-acting antiretroviral drugs includes: Ibalizumab and Leronlimab (monoclonal Antibody), Rilpivirine (NNRTI), cabotegavir (INSTI), Islatravir (NRTTI)[94].

ART Metabolism

In general, guidelines for naive HIV patients recommend the combination of three active drugs to prevent the occurrence of resistance: a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with either an NNRTI or a PI boosted with ritonavir, or an integrase strand transfer inhibitor (INTI). The US Department of Health and Human Services (DHHS) procedure recommends ART for all HIV-1 patients with a CD4 count ≤200 cells/μL and HIV RNA >100,000 copies/mL to preserve or improve immune function and to decrease HIV-associated morbidity and mortality. Similar regimens should be used in PLWH according to the treatment plan (AC, radiotherapy or surgery), the presence of liver or renal diseases, bone marrow suppression, mitochondrial dysfunction and patient preference[95]. The simultaneous use of ART and AC could be connected with an amplified risk of toxicity due to pharmacokinetic and pharmacodynamic interactions mediated by drug-metabolizing enzymes. It is noteworthy that the majority of antiretroviral drugs are CYP 450 substrates, either inducers or inhibitors. Because many antineoplastic molecules are also metabolized by the cytochrome P-450 (CYP450) system, co-administration with ART could result not only in drug accumulation and possible toxicity but also in a decrease in the efficacy of one or both classes of drugs[96-98]. In particular, drugs that inhibit CYP450-enzymes typically cause decreased metabolism of other drugs that are metabolized by the same enzyme (Table I). Decreased metabolism can result in elevated drug levels and increased toxicity. Inhibition of CYP450 is rapid, with the maximal inhibitory effect occurring when steady-state concentrations of the inhibitor are established. Conversely, induction of the CYP450 system results in the increased clearance of drugs that are simultaneously metabolized by the same enzyme and a consequent decrease in the drug concentration. Enzyme induction occurs more slowly than inhibition because of the full effect of the drug on the time needed for new enzyme synthesis and the $T_{1/2}$ (half-life) of the inducer agent[92]. In this superfamily, 57 genes and 58 pseudogenes have been identified, which are divided into 18 families and 43 subfamilies. Among them, three sub-families of CYPs, including CYP1, CYP2, and CYP3, contribute to the metabolism of more than 93% of ART and AC therapies[99].

Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

For NRTIs, the potential for DDIs is minimal because these agents are not metabolized by the CYP 450 system, and they are not inducers or inhibitors of CYP 450 enzymes. However, NR-

Table I. Summary of Pharmacokinetic of ART drug class.

HAART drug Class	Metabolic fate	Hepatic Inhibitors	Hepatic Inducer	Pharmacogenomics evidence
NRTIs	Several Nucleosidase Abacavir Tenofovir,	No Evidence	No Evidence	Screening for HLA-B*5701 For prevention of the hypersensitivity to Abacavir [92]. Tenofovir Neprho- Toxicity in carriers of ABCC4 3436GG [93].
NNRTIs	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor)	Efavirenz: CYP2C9, CYP2C19 . Etravirine11: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine 20; 3A4 (potent)	Efavirenz: 3A4 (potent), 2B622, UGT1A123 Etravirine11: 3A4 (weak) Nevirapine12: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak). 24 A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.13	Nevirapine and Efavirenz Neurotoxicity in CYP2B6*6 (516G>T) homozygous individuals [14]. Nevirapine hepatotoxicity in polymorphic ABCB1 3435CC allele (MDR1 C3435T) [94].
PIs	Mainly CYP3A4 and UGT1A1/3	darunavir, indinavir, nelfinavir, amprenavir >> saquinavir Atazanavir: 3A4, UGT1A1 >>2C8 (weak) Caution when unboosted atazanavir is coadministered with drugs that are CYP2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir. Nelfinavir: CYP2B6 *in vitro*. Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1. At small boosting doses, ritonavir has a negligible The effect of CYP2D6 inhibition. Ritonavir inhibits CYP2B6 *in vitro* but induces 2B6 *in vivo*. Tipranavir: CYP2D6	Nelfinavir: UGT, 2B6, 2C8, 2C9/19 Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir	Favorable response (in term of viral suppression) to Nelfinavir in CYP2C19*2 and *3 poor metabolizer patients [92]. Decreased clearance of, indinavir and saquinavir in haplotype CYP3A5*3. [93]. Lopinavir plasma levels are higher in SLCO1B1 521CC allele than 521TT [100]. High level of bilirubinemia among patients homozygous for the UGT1A1*28 for indinavir and Atazanavir administration [100].

Table continued

Table I *(Continued)*. Summary of Pharmacokinetic of ART drug class.

HAART drug Class	Metabolic fate	Hepatic Inhibitors	Hepatic Inducer	Pharmacogenomics evidence
INSTIs	Dolutegravir: UGT1A1, CYP3A4 (10-15%). Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, CYP 2D6 (minor) Raltegravir: UGT1A1	Cobicistat: CYP3A, CYP2D6; also P-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. Dolutegravir inhibits the renal organic cation transporter, OCT2.	Dolutegravir and Cabotegavir does not induce CYP1A2, CYP2B6, or CYP3A4 *in vitro*. (103) Elvitegravir: CYP2C9 (modest)	
CCR5 receptor antagonists	Maraviroc: CYP3A family	No Evidence	No Evidence	evidence of increased risk of susceptibility to hepatitis C virus infection or multiple sclerosis among individuals with CCR5-delta32 mutation [104]
Fusion Inhibitors	Enfuvirtide is ligand for viral gp41	No Evidence	No Evidence	

ABCC, ATP-binding Cassette; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter, novel type; SLC, solute carrier; SLCO, solute carrier organic anion.

TIs may be the target of transporter-mediated interactions because the renal pathway is their primary route of elimination. Tenofovir can lead to renal dysfunction, particularly in patients receiving nephrotoxic drugs. Renal function should be monitored over time, and the dose adapted in the case of renal injury. In patients treated with abacavir (ABC), genotypic screening for HLA-B* 57.01 should be performed to reduce the risk of a hypersensitivity reaction to ABC[97]. Current data have shown a susceptibility locus within the B*57.01 HLA-DR7 haplotype, which was present in approximately 95% of patients with ABC hypersensitivity[98].

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

The NNRTI molecules are widely metabolized *via* the CYP450 enzyme[92]. The potential for DDIs is high because these agents are extensively metabolized by the CYP450 system[92]. These regimens are associated with several adverse events including rash, central nervous system (CNS) toxicity, and elevation of hepatic transaminase plasma levels. CNS side effects have been noted in up to 50% of patients but are sufficiently severe to require discontinuation in approximately 4% of cases. There is a potential toxic additive effect with alcohol and neuroactive drugs. Nevirapine acts as an inducer of CYP3A4, and Efavirenz can either inhibit or induce CYP3A4 enzyme activity. Efavirenz frequently acts as a CYP3A4 and CYP2B6 inducer[100]. Etravirine, a second generation NNRTI, is a weak inducer of CYP3A and a weak inhibitor of P-glycoprotein and constitutes an important choice for concomitant use with BEACOPP chemotherapy for advanced HD. Rilpivirine is primarily metabolized by the CYP3A complex and does not induce CYP450[100].

Protease Inhibitors (PIs)

PIs are strong CYP450 inhibitors[101]. Ritonavir (RTV) is the most potent CYP3A4 inhibitor and is an active inhibitor of CYP2C8, CYP2D6 and ABCB1 and a weak inducer of CYP2B6, CYP2C9, CYP3A4, and ABCB1. Second-generation PIs (atazanavir, darunavir, fosamprenavir, lopinavir, and tipranavir) are efficiently active against HIV acquired variants that have developed resistance. PI regimens are associat-

ed with adverse events such as gastrointestinal symptoms, dyslipidemia, insulin resistance, hepatic transaminase elevation, and an augmented risk of cardiovascular events. Hepatotoxicity is more frequent and more severe with a full dose of RTV than with other PIs. The lower RTV doses in dual-PI combinations reduce the overall risk. QT extension has been related, in particular, to PIs such as atazanavir, saquinavir and ritonavir-boosted lopinavir[102].

Integrase Inhibitors (INSTIs)

INSTIs are a class of drug with diverse metabolic routes. Raltegravir, the first approved INSTI, is metabolized only by UDP-glucuronosyltransferase-1A1 (UGTA1A1) and is unlikely to have major interactions. Raltegravir is neither an inhibitor nor an inducer of CYP450 enzymes, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and does not inhibit P-glycoprotein-=mediated drug transportation. Consequently, it can be an alternative choice for the prevention of DDI with AC agents[100]. It has been associated with variability in creatine kinase plasma levels, myopathy, and rhabdomyolysis. Elvitegravir is primarily metabolized by cytochrome CYP3A4/5 and partly by glucuronidation *via* UGT1A1/3 and is a component of an FDA-approved fixed-dose combination tablet (Stribild) containing tenofovir alafenamide, emtricitabine, and the CYP3A4 inhibitor cobicistat. Dolutegravir has a minor role with CYP3A4 because it is metabolized by UGTA1A1. Promising is recently approved congener of dolutegavir, cabotegavir with minor side effects like insomnia, headache, allergic reactions. Both, present abnormal liver function in patients who are concomitant hepatitis B or C with augmented serum creatinine levels due to inhibition of the renal-tubular secretion of creatinine[103].

CCR5 Receptor Antagonists

CCR5 receptor antagonists are a group of small molecules that antagonize the CCR5 receptor. The CCR5 antagonist maraviroc is a substrate of CYP3A and ABCB1 but does not alter metabolism or transport. Leronlimab is a recent new entry in CCR5 receptor antagonist. It seems to have lower adverse events include hepatotoxicity, pyrexia, rash, and upper respiratory tract infections[104].

Fusion Inhibitors

Fusion inhibitors, in particular Enfuvirtide, are not metabolized by CYP450 but undergo hydrolysis. To date, no DDIs have been registered. Side effects related to enfuvirtide include diarrhea, fatigue, nausea, and injection site reactions[97].

DDIs Between AC and Art Based on Pharmacogenomics

Promising drug interaction based on individual genomic profiles should allow the prediction of the toxicity/inefficacy of ART/AC combined therapy (**Supplementary Table I**). It is well acknowledged that the response to chemotherapy depends on the individual metabolic profile *via* the CYP450 route and the CYP450 extra-route[104,105]. More examples are represented by the neurological effect of FOLFOX therapy that could be predicted by a pharmacogenomic panel performed before therapy, as well as the lethal effect of the DPYD risk genetic variant. In addition, therapy based on cytarabine and its related drug Gemcitabine is affected by several polymorphisms found in the Cytidine Deaminase (*CDA*) gene[106-108].

Variability between patients in relation to the bioavailability and distribution of ART regimens is probably driven by genetic and environmental factors such as body weight, drug-food interactions, and sex. In particular, DDIs and genetic polymorphisms in drug-metabolizing enzymes and drug transporters contribute to widespread variability in drug pharmacokinetics, response to therapy, and toxicity. A few examples are reported below. Although the response to ART is highly complex and often limited by the development of short- or long-term toxicities and the emergence of antiretroviral drug resistance, this variability could be explained by factors that standardize the availability of drugs (pharmacokinetics), effects on the host (host pharmacodynamics), and the activity of the virus itself (viral pharmacodynamics).

The observance of dose-schedule and dose-intensity is a primary goal to treat cancer. The timing of diagnoses of HIV and a tumor must guide therapeutic decisions. In some cases, cancer treatment should take priority over ART, despite the risk associated with stopping HIV treatment. However, ART is always recommended, especially if a patient is diagnosed with HIV and malignancy, to prevent the emergence of resistant HIV strains and opportunistic infections[95,97]. Mutagen-

Table II. High points.

Highlights Box
Among cancers recorded in HIV patients, it is possible to distinguish AIDS-defining cancers (ADCs), such as Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and invasive cervical cancer, and non-AIDS-defining cancers (NADCs), including hepatocellular carcinoma (HCC), anal cancer, lung cancer, colorectal cancer (CRC), gastrointestinal cancer (GI), breast cancer and Hodgkin's lymphoma (HL). Here, we reviewed in detail the most recent data on NDACs.
The first obstacle for the oncologist to plan treatment for cancer in HIV-patients is the preliminary evaluation of drug-drug interactions between AC and ART. Recent progress in pharmacogenomic fields could provide a new approach to personalized therapy.
The same adverse drug reaction related to ART/AC combined treatment could be predicted through genetic polymorphisms known to be involved in their biotransformation.
The pharmacogenetic testing for polymorphisms in CYP450 genes could help the oncologist stratify patients who are most likely to have a better outcome with ART/AC (Table I).
Even if there is a clinical utility for detecting CYP450 polymorphisms involved in ART-based therapy, whether pharmacogenomics testing improves clinical outcomes is still an open question.
The importance of cooperation between oncologists and other health specialists (i.e., infectious disease, pharmacogenetic and lab specialists) must not be underestimated in order to maximize the clinical management of HIV in cancer patients.

esis in the viral genome is a continuous process that occurs in each replication cycle, enabling the virus to adapt quickly. A list of the primary viral resistances against ART is available in Shafer[101].

The accessibility of more than 20 approved antiretroviral drugs and the opportunity for individual genotype profiling allows the development of regimens that minimize potential DDIs and improve compliance with ART during AC therapy[97,107-109]. Anthracyclines, antimetabolite agents, antitumor antibiotics, and platinum agents undergo non-CYP450 routes of elimination and are unlikely to be altered by ART. Camptothecins undergo UGTA1A1-enzymatic routes and are not inhibitors or inducers of CYP450 isozymes and, therefore, are likely to be altered by ART[92]. On the other hand, DDIs can be anticipated with alkylating agents, corticosteroids, epipodophyllotoxins, taxanes, tyrosine-kinase inhibitors and vinca alkaloids (**Supplementary Table II**).

The *CYP2B6* gene is extremely polymorphic, and more than 28 alleles have been characterized (approximately 100 SNPs). Among these variants, the *CYP2B6*6* haplotype (*516 G>T*, and *785A>G*) leads to reduced catalytic activity. Several studies[105.107,110] have reported neurotoxicity using Nevirapine and Efavirenz in CYP2B6*6 (516G>T) homozygous individuals. Several polymorphisms of the *CYP2C19* gene are associated with reduced enzyme activity. In particular, the *CYP2C19*2* allele leads to a 681G>A substitution, causing a stop codon splicing variant. These poor metabolizing patients have a favorable response (in terms of viral suppression) using Nelfinavir[110]. Variability in metabolic CYP3A5 function is mainly attributed to the *CYP3A5*3* mutant allele and, to a lesser degree, to the *CYP3A5*6* and *CYP3A5*7* variants. The variant *CYP3A5*3* allele produces an alternate mRNA splicing, resulting in an aberrant protein due to the creation of a premature stop codon[111]. Haplotype *CYP3A5*3* has been associated with appreciably decreased clearance of both indinavir and saquinavir[112]. The CCR5 antagonist maraviroc is a substrate of CYP3A and ABCB1. It has been associated with hepatotoxicity and infections among individuals with CCR5-Delta32 mutations[113]. Correlations between polymorphisms in the ATP-binding Cassette (*ABCC*) and efficacy of therapy were also found; likewise, drug transporters are seen as one of the primary mechanisms that account for suboptimal tissue concentrations of ART and AC. Major studies[111-113] reported an association between the *ABCB1* polymorphism (*3435 C>T*) and the overall risk of hepatotoxicity after nevirapine treatment. This genotype-phenotype association was established by Ritchie et al[103], who showed that the *ABCB1 3435 TT* allele was infrequent in the patient group displaying hepatic toxicity compared to those with polymorphic *3435CC*. However, a pharmacogenetic study that integrated the *C421A* and *G34A* variants that were associated *in vitro* with a decrease in ABCG2 activity found no association of these polymorphisms with the intracellular concentration of zidovudine triphosphate and lamivudine triphosphate. Few studies[113,114] are available on other nucleoside analogs. Current data suggest an important role for influx *via* the Solute Carrier Organic Transporters (SLCO alias OATP) family in the pharmacokinetics of ART.

In detail, it has been observed that the *SLCO1B1 521T>C* variant was considerably related to higher plasma concentrations of lopinavir in patients homozygous for the mutant allele (*521CC*). This suggests that the influx of lopinavir into the liver *via* the SLCO1A2 influx transporter is a central issue of exposure to lopinavir[113]. Recent studies in patients who received atazanavir and indinavir recognized that the proportion of grade 3 to 4 hyperbilirubinemia was 80% among patients homozygous for the *UGT1A1*28* allele, 29% in heterozygous patients and 18% in patients homozygous for the wild type allele[114,115] (Table II).

Conclusions

In the ART era, PLWH are living longer. Considering that the incidence of most malignancies increases with age, they have a greater risk of developing cancer. In addition to prolonged survival, the incidence of NADCs may be significantly influenced by behavioral risk factors, such as intravenous drug use and smoking. The GICAT has demonstrated that the multidisciplinary approach in this particular setting of patients is the best way to obtain good and safe results[6]. Patients who receive a combination of AC and ART can achieve better response and survival rates than patients who receive AC alone. However, careful attention must be paid to cross toxicity and possible pharmacokinetic and pharmacodynamic interactions between antiretroviral drugs and AC[116,117]. All PIs are inhibitors of CYP3A, which is important in the metabolism of approximately 50% of all AC drugs. Among the PIs, ritonavir and cobicistat are the strongest inhibitors of CYP3A4. Conversely, NNRTIs can induce metabolism and potentially reduce the efficacy of AC drugs. Although raltegravir has little potential for DDIs, the presence of viral mutations limits its use as a single agent. Interactions can also be a result of a modification of the activities of glucuronosyltransferases and/or of transport proteins. Ritonavir is an inhibitor of P-glycoprotein, which leads to increased exposure to many antineoplastic drugs. Zidovudine is associated with severe neutropenia and should not be combined with cytotoxic regimens containing neutropenic agents. Didanosine and stavudine, older generation NRTIs, are associated with irreversible peripheral neuropathy, which is also a common side effect of platinum salts, taxanes, vinca alkaloids and bortezomib. AC-induced neuropathy is generally cumulative or dose-related, with management consisting of dose-reduction or lower dose-intensity. PIs and newer targeted anti-cancer agents including tyrosine kinase inhibitors can cause QT prolongation, arrhythmias, and sudden death. In addition, PIs appear to significantly potentiate the myelotoxicity of AC. Bilirubin is often used as a guide for dose adjustment for AC agents such as docetaxel, doxorubicin, etoposide, irinotecan, paclitaxel, sorafenib, and vincristine. Several antiretroviral drugs such as atazanavir and indinavir are associated with unconjugated hyperbilirubinemia secondary to UGT1A1 inhibition similar to that which occurs in Gilbert's syndrome. If no other signs of liver dysfunction exist, dose modifications of AC based on liver function tests can be ignored. Generally, to prevent DDIs and avoid severe toxicity, treatment options include substitution of an antiretroviral alternative or temporary discontinuation of ART or selection of an alternative chemotherapy regimen. In conclusion, we account that HIV treatment has entered a new era in which multidrug treatments and genetic variations (host and virus) must be taken into consideration when formulating chemotherapeutic/HAART regimens, in order to maximize benefits and minimize toxicity. Finally, it is important that patients with cancer should be screened for HIV infection, and treatment of HIV infection should be started immediately.

In this scenario, has not to be underestimated the cooperation importance between oncologists and other health specialists (i.e., infectious disease, pharmaco-genetists and lab specialists), in the management of these patients aimed at an adequate treatment strategy.

Moreover, we suggest you pay attention to the use of natural products, concomitant with ART and antitumor drugs, very common in cancer and chronic patients, with the aim to contrast the long side effects as cancer related fatigue[118-124].

Current guidelines for naive HIV patients recommend the combination of three active drugs to prevent the occurrence of resistance: a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with either an NNRTI or a PI boosted with ritonavir, or an integrase strand transfer inhibitor (INTI).

It is known that ART increases NADCs in longer lived patients[3]. The longer duration of HIV infection and a history of repeated opportunistic infections are also considered as relevant risk factors for NADCs. Moreover, cancer risk is higher in HIV+ patients compared to the general population, partly as a consequence of the high prev-

alence of cancer risk factors, such as smoking, alcohol consumption, HPV and HCV infection among HIV+ people[10,11].

The accessibility of more than 20 approved antiretroviral drugs and the opportunity of individual genotype profiling allows the adaptation of better regimens that minimize the potential DDIs and improve compliance with ART during AC therapy.

ART should be individualized according to the cancer treatment plan (AC or radiotherapy or surgery), liver or renal diseases, bone marrow suppression, mitochondrial dysfunction, and individual patient genotype, all according to validated pharmacogenomics tests[125]. In fact, the cost-effectiveness of testing is still unknown, and clinical expertise on understanding the laboratory results is urgently needed[126,127]. In this scenario, the importance of collaboration between oncologists and other health specialists (i.e., infectivologists, pharmacists, geneticists, and lab specialists) must not be underestimated in the management of these patients, with the aim to design an adequate treatment strategy, also in the COVID-era[128,129].

We can safely say that ART has given dignity to patients with HIV. The new challenge is combining ART with other therapies. In oncology, the results are promising thanks to the knowledge of the individual genomic profile.

The largest bias of the ART/AC therapeutic approach is that it is currently applied only in some countries. The future goal will be to bring this therapeutic practice to a place where the number of HIV patients is more elevated (i.e., Africa).

Conflict of Interest
The Authors declare that they have no conflict of interests.

Authors' Contributions
Conceptualization and design, MB, BAF, MM, GM, ADV; methodology MB, BAF, MM, GM, ADV; original draft preparation and writing: MB, BAF, MM, RDF, GM, ADV; review and editing: MB, BAF, MM, RDF, GM, ADV. All authors have read and agreed to the published version of the manuscript.

Funding
No funding was received for this study.

Ethics Approval
Not applicable.

Informed Consent
Not applicable.

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Reference annotations. Papers of particular interest should be identified using one or two asterisk symbols: * = of interest; ** = of considerable interest