Supplementary Material

Search strategy and selection criteria

Publications reviewed herein were selected from papers identified by MEDLINE searches. MeSH terms used were: “cancer” or “neoplasm” or “malignancy” AND “autophagy.” These were paired with each of the following terms: “antiretroviral drug,” “HIV protease inhibitor,” “integrase inhibitor”, “reverse transcriptase inhibitor,” “Ibalizumab,” “Fostemsavir,” “Cenicriviroc,” “Enfuvirtide,” “Lenacapavir,” “Zidovudine,” “Didanosine,” “Zalcitabine,” “Stavudine,” “Lamivudine,” “Abacavir,” “Tenofovir,” “Emtricitabine,” “Dapivirine,” “Nevirapine,” “Delavirdine,” “Efavirenz,” “Etravirine,” “Rilpivirine,” “Doravirine,” Islatravir,” “Raltegravir,” “Elvitegravir,” “Dolutegravir,” “Bictegravir,” “Cabotegravir,” “Saquinavir,” “Indinavir,” “Nelfinavir,” “Ritonavir,” “Lopinavir,” “Amprenavir,” ”Atazanavir,” “Fosamprenavir,” “Tipranavir,” or “Darunavir.” Articles chosen for inclusion were those that performed any experiment to evaluate autophagy after treatment with an antiretroviral drug or an analog of an antiretroviral drug in the context specifically of a cancer model, unless the drug or analog was used for direct antiviral effects such as in malignancies related to Acquired Immunodeficiency Syndrome, Human T-lymphotropic virus-1, Human Herpesvirus 8, Epstein-Barr virus, or Hepatitis B Virus. Other references were chosen for relevancy to the immediate topic. Only papers published in the English language were included.

Supplemental Table 1. Examples of the anti-tumor effects of antiretroviral drugs.

Antiretroviral drug	Effects leading to cancer cell death	Ref.
Entry Inhibitors		
Cenicriviroc	Inhibits chemokine signaling; inhibits angiogenesis	[1-3]
Ibalizumab (modified)	Inhibits TGF[1]-β	[4]
Maraviroc	Causes cell cycle arrest; reduces macrophage accumulation in tumors; inhibits angiogenesis; chemosensitizer; inhibits CCR5[2] signaling	[2, 5-9]
Rev. Transc. Inhib.		
Abacavir	Decreases cell migration; inhibits cell proliferation; radiosensitizer	[10-12]
Didanosine (modified)	Decreases cell proliferation; causes DNA damage	[13]
Doravirine	Decreases cell migration; causes cell cycle arrest	[14]
Efavirenz	Causes oxidative and mitochondrial stress; radiosensitizer; decreases metabolic activity; causes DNA damage; causes mitochondrial damage	[15-22]
Emtricitabine	Causes DNA damage; causes cell cycle arrest	[23]
Etravirine	Causes cell cycle arrest; causes DNA damage; decreases cell viability	[22, 24]
Lamivudine	Decreases cell migration; inhibits cell proliferation; causes cell cycle arrest; radiosensitizer	[10, 11, 14, 25]
Nevirapine	Decreases cell migration; causes DNA damage	[26, 27]
Rilpivirine	Decreases cell viability; causes cell cycle arrest	[24, 28]
Stavudine	Causes DNA damage; induces oxidative stress; inhibits cell proliferation; inhibits LINE-1[3] retrotransposition	[10, 21, 29]
Tenofovir	Causes DNA damage; causes cell cycle arrest; decreases cell migration; inhibits LINE-1 retrotransposition	[10, 22, 23, 29-31]
Zalcitabine	Radiosensitizer	[32]
Zidovudine	Inhibits DNA polymerase; decreases metabolic activity; causes mitochondrial damage; inhibits LINE-1 retrotransposition chemosensitizer; radiosensitizer	[11, 20, 21, 29, 33, 34]
Integrase Inhibitors		
Cabotegravir	Decreases cell migration	[14]
Dolutegravir (modified)	Perturbs intracellular calcium levels; inhibits cell proliferation	[35, 36]
Elvitegravir	Inhibits metastasis	[37]
Raltegravir	Decreases cell migration	[38]
Protease Inhibitors		
Amprenavir	Inhibits p-AKT[4], ERK1/2[5] signaling	[39, 40]
Atazanavir	Causes ER[6] stress; inhibits cell proliferation	[41, 42]
Darunavir	Decreases cell viability	[24]
Indinavir	Decreases MMP[7] secretion and MMP activity; inhibits angiogenesis; restores T-cell responsiveness	[43-45]
Lopinavir	Causes ER stress; induces cell cycle arrest; inhibits cell proliferation; causes oxidative stress; inhibits cell proliferation; chemosensitizer	[19, 42, 46-48]
Nelfinavir	Inhibits the proteosome; causes ER and mitochondrial stress; causes cell cycle arrest; radiosensitizer; chemosensitizer	[41, 46, 49-53]
Ritonavir	Inhibits the proteosome; causes cell cycle arrest; changes T-cell epitope processing; inhibits angiogenesis; inhibits cell proliferation	[19, 42, 54-56]
Saquinavir	Restores T-cell responsiveness; inhibits the proteosome; inhibits p-AKT; inhibits angiogenesis	[45, 57, 58]
Tipranavir	Chemosensitizer; inhibits cell proliferation	[59, 60]

[1]Transforming growth factor; [2]C-C chemokine receptor type 5; [3]Long interspersed element-1; [4]Protein Kinase B; [5]Extracellular signal-regulated kinase 1/2; [6]Endoplasmic reticulum; [7]Matrix Metalloprotease

Supplemental Table 2. Clinical trials of antiretroviral drugs as chemotherapeutic agents registered at clinicaltrials.gov[1].

Antiretroviral drug	Malignancy	NCT[2] Number	Phase	Status	Accompanying treatments
Entry Inhibitors					
Maraviroc	Colorectal, liver	NCT01736813	Observational	Completed	
	Colorectal, pancreatic	NCT04721301	I	Completed	w/ two biologics
	Colorectal	NCT03274804	I	Completed	w/ pembrolizumab
Rev. Transc. Inhib.					
Efavirenz	Solid tumors or NHL[3]	NCT01878890	I	Completed	
	Prostate	NCT00964002	II	Completed	
	Pancreatic	NCT00964171	II	Unknown	
	Breast	NCT05076682	II	Recruiting	w/CT, anti-PD[12]-1 antibody
Lamivudine	SCLC[4]	NCT04696575	II	Recruiting	w/ platinum-based CT[13]
	p53-mutant colon	NCT03144804	II	Completed	
Zidovudine	Adult T-cell	NCT02737046	II	Recruiting	w/ belinostat, IFN[14]-α-2b
	Adult-T-cell	NCT01941680	Observational	Completed	w/ polyCT, pegylated IFN
	KSHV[5]-associated MCD[6]	NCT00092222	II	Active	
Integrase Inhibitors					
Raltegravir	SCC[7] of head and neck	NCT01275183	Early I	Completed	w/ cisplatin
Protease Inhibitors					
Atazanavir	Solid tumors, hematologic	NCT04184869	Extension	Completed	w/ belinostat
Indinavir	Pediatric sarcoma	NCT00001566	II	Completed	w/ autologous T-cell transplant
Indinavir/Ritonavir	Tumors w/ brain metastases	NCT00637637	II	Unknown	w/ EBRT[15]
Nelfinavir	Solid tumors, or prostate	NCT05036226	I/II	Recruiting	w/ COAST[16]
	Vulvar	NCT04169763	I	Recruiting	w/ cisplatin, EBRT
	MM[8]	NCT03829020	I	Active	w/ bortezomib, metformin
	Solid tumor or lymphoma	NCT03422874	I	Withdrawn	w/ MLN9708
	Cervical	NCT03256916	III	Recruiting	w/ cisplatin, pelvic EBRT
	Melanoma, lung or kidney	NCT03050060	II	Terminated	w/ a biologic, RT[17]
	Cervical	NCT02363829	I	Completed	w/ cisplatin, RT
	Head and neck SCC	NCT02207439	II	Completed	w/ CT, RT
	MM	NCT02188537	II	Completed	w/ bortezomib, dexamethasone
	Pancreatic	NCT02024009	I/II	Unknown	w/ polyCT, RT
	Pancreatic	NCT01959672	II	Completed	w/ polyCT, RT
	CIN[9] 2/3 or CIN3	NCT01925378	II	Withdrawn	
	Progressive MM	NCT01555281	I/II	Terminated	w/ lenalidomide, dexamethasone
	Cervical	NCT01485731	I	Completed	w/ cisplatin, pelvic RT
	NSCLC[10]	NCT01447589	I/II	Withdrawn	w/ radical RT
	Solid tumors	NCT01445106	I	Completed	
	Hematologic	NCT01164709	I	Completed	w/ bortezomib
	NSCLC	NCT01108666	II	Terminated	w/ CT, proton beam RT
	Pancreatic	NCT01086332	I	Terminated	w/ gemcitabine, RT
	Any	NCT01079286	I	Completed	w/ temsirolimus
	Pancreatic	NCT01068327	I	Completed	w/ polyCT, RT
	Adenoid cystic	NCT01065844	II	Completed	
	Glioblastoma	NCT01020292	I	Completed	w/ CT, RT
	Glioblastoma	NCT00915694	I	Terminated	w/ temozolomide, RT
	NSCLC	NCT00791336	II	Terminated	w/ CT, RT
	Rectal	NCT00704600	I/II	Completed	w/ CT, RT
	Glioblastoma	NCT00694837	I	Completed	w/ temozolomide, CT, RT
	NSCLC	NCT00589056	I/II	Completed	w/ polyCT, thoracic RT
	Liposarcoma	NCT00233948	I/II	Terminated	
Ritonavir	Breast	NCT05150691	I/IIa	Recruiting	
	Melanoma, CLL[11]	NCT02948283	I	Completed	w/ metformin
	Glioblastoma	NCT02770378	I/II	Completed	w/ temozolomide, polyCT
	Breast	NCT01009437	I	Completed	
Ritonavir/Lopinavir	Gliomas	NCT01095094	II	Terminated	

[1]This table includes only trials registered at clinicaltrials.gov. It does not include investigator-initiated studies, those not intended for Federal Drug Administration approval or package insert changes, or others that may be self-funded at an institution, by foundations, or by certain government agencies that are not registered at clinicaltrials.gov. This review is focused on the benefits of the off-target effects of antiretroviral drugs; therefore, this table also does not include trials of antiretroviral drugs: 1) when the drug is being used for a direct antiviral effect as in treatment of Acquired

Immunodeficiency Syndrome, Human T-lymphotropic virus-1, Human Herpesvirus 8, Epstein-Barr virus, or Hepatitis B Virus (HBV) related malignancies; 2) for prophylaxis of HBV reactivation in the setting of receiving chemotherapy; 3) when Ritonavir is being used to boost chemotherapy drug levels by its action on cytochrome P450(CYP3A); 4) for pharmacokinetic studies in healthy subjects. [2]National Clinical Trial; [3]Non-Hodgkin's lymphoma; [4]Small cell lung cancer; [5]Kaposi's sarcoma herpesvirus; [6]Multicentric Castleman's disease; [7]Squamous cell carcinoma; [8]Multiple Myeloma; [9]Cervical intraepithelial neoplasia; [10]Non-small cell lung cancer; [11]Chronic lymphocytic leukemia; [12]Programmed death protein 1; [13]Chemotherapy; [14]Interferon; [15]External beam radiation therapy; [16]Combination of autophagy selective therapeutics; [17]Radiation therapy

References for Supplemental Table 1

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