J Immunol Clin Microbiol
Available online at: https://dergipark.org.tr/tr/pub/jicm
DOI: 10.58854/jicm.1914016

Journal of Immunology and Clinical Microbiology

REVIEW / DERLEME

Ovarian Cancer in Women Living With HIV: Epidemiology, Mechanisms, and Clinical Management

HIV ile Yaşayan Kadınlarda Over Kanseri: Epidemiyoloji, Mekanizmalar ve Klinik Yönetim

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Received: 22.03.2026, Accepted:25.05.2026

Abstract

The growing concern over the intersection of ovarian cancer [OC] and Human Immunodeficiency Virus [HIV] among women has prompted considerable scientific inquiry into the possible implications of HIV for the incidence of ovarian malignancies. This review explores the occurrence of OC in HIV-positive women, examining the multifaceted pathophysiological interactions that may contribute to ovarian tumorigenesis in this population. The primary aim of the research is to evaluate the possible association between HIV infection and OC development, with a focus on immune dysfunction, viral load, and antiretroviral therapy as potential contributors. This review synthesizes findings from epidemiological studies, clinical trials, and laboratory investigations to highlight the complex interplay of immunosuppression and cancerogenesis in the context of HIV infection. The significance of this work lies in its potential to inform targeted healthcare strategies and interventions for HIV-positive women, addressing both cancer prevention and management in this vulnerable group. Methodologically, this review assesses the results of a comprehensive analysis of cross-sectional studies, cohort data, and case-control studies to evaluate the relationship between HIV and OC risk. The findings suggest that the association between HIV and OC remains incompletely understood, as the available evidence is limited, heterogeneous, and largely observational; possible contributing factors may include chronic inflammation, immune suppression, and long-term antiretroviral drug use. These findings contribute to a deeper understanding of the intersection of viral infections and cancer risk, with important implications for future research and public health policy. The practical significance of this research lies in its potential to support clinical awareness and improve recognition of this underexplored issue in HIV-positive women.

Keywords: Ovarian Cancer, HIV-positive Women, Cancer Risk, Immune Dysfunction, Antiretroviral Therapy

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How to Cite: Hejran AB, Niazi P. Ovarian Cancer in Women Living With HIV: Epidemiology, Mechanisms, and Clinical Management. *Journal of Immunology and Clinical Microbiology* 2026;11(2):140-93

INTRODUCTION

Ovarian cancer (OC) remains one of the most lethal malignancies affecting women worldwide, HIV-positive women, with their increased life expectancy due to highly active antiretroviral therapy (HAART), face a growing risk of non-AIDS-defining gynecologic cancers, including ovarian cancer (1, 2, 3, 4, 5). The group of risk factors includes older age along with BRCA1/2 mutations and hereditary background combined with specific reproductive characteristics (6, 7, 8, 9, 10, 11). Simultaneously, Human Immunodeficiency Virus (HIV) remains a formidable global health concern, exerting a disproportionate burden on women. As of 2022, females constituted nearly 53% of the 39 million individuals diagnosed with HIV across the globe (12, 13). In regions such as Sub-Saharan Africa, women and girls constitute 63% of newly reported HIV cases, highlighting the disproportionate burden of the epidemic on female health. The virus debilitates the immune system, heightening vulnerability to opportunistic infections and neoplastic diseases (14, 15). Examining the nexus between HIV and OC is of paramount importance due to the potential exacerbation of health risks. Women living with HIV may encounter distinct gynecological complications, including an elevated predisposition to specific malignancies (16, 17, 18). In 2012, there were 239,000 newly diagnosed cases of ovarian cancer globally, alongside 152,000 deaths attributed to the disease. Despite some progress in survival rates, 60% of women in the United States are diagnosed with ovarian cancer only after the disease has spread, resulting in a dismal 5-year survival rate of 29%. OC continues to be the leading cause of mortality from gynecologic malignancies in the U.S. The majority of ovarian cancers are of epithelial origin, classified as epithelial ovarian cancers (EOCs). Invasive EOCs comprise 90% of cases and are categorized into five distinct histopathological subtypes: high-grade serous (HGSOC), low-grade serous (LGSOC), endometrioid (ENOC), clear cell (CCOC), and mucinous (MOC). Borderline EOCs, characterized by the absence of stromal invasion, include two histotypes: serous and mucinous. Endometriosis, defined as the presence of ectopic endometrial tissue, serves as the precursor for ENOC and CCOC (Table 1) (19, 20, 21, 22, 23, 24, 25, 26, 27, 28).

The study by Dilley et al. (2020) investigated how diagnosis interval and route affect postmenopausal women with invasive epithelial tubo-ovarian cancer (iEOC) in the UK Collaborative Trial of OC Screening (UKCTOCS). The survival rates of patients were significantly worse for women who displayed National Institute for Health and Care Excellence (NICE) symptoms included in the modified Goff Index during diagnosis. Each new symptom presented by patients corresponded to a shorter lifespan. The analysis showed that patients with advanced stage cancer along with rising residual disease presence, insufficient initial treatment or painful abdomen and appetite loss displayed elevated mortality risk (29, 30, 31). And a study evaluated the accuracy of a self-reported measure of undetectable viral load (VL) in Canadian women living with HIV. The findings revealed that 85% of participants reported having an undetectable VL, while 82% had clinical evidence confirming viral suppression. The self-reported data was highly predictive of actual viral suppression in this population of Canadian women with HIV (32, 27).

OC remains a highly lethal malignancy among women. OC, the eighth most prevalent malignancy among women worldwide, is a multifaceted neoplasm that affects the ovaries, fallopian tubes, and peritoneal cavity. In 2018, OC was linked to 295,414 new cases, 184,799 fatalities, and 762,663 instances with a five-year survival rate. The highest incidence and mortality rates are observed in Asian nations, followed by European

countries. The unfavorable prognosis of OC is primarily attributed to a deficient comprehension of its molecular underpinnings and the overlap of its symptoms with those of other medical conditions. In its nascent stages, OC frequently manifests as tubal intraepithelial carcinoma (TIC); however, the precise mechanisms governing its initiation and progression to invasive disease remain elusive. Recent advancements in genomics and proteomics have significantly enhanced the identification of biomarkers and the refinement of screening methodologies, facilitating early detection (33, 34, 35, 36, 37, 38, 39).

Recent studies prove microbial infections function as major cancer-causing risk elements responsible for approximately 15%–20% of total cancer occurrences. The International Agency for Research on Cancer (IARC) identifies human papillomavirus (HPV) and hepatitis B and C viruses (HBV and HCV) as well as human T-lymphotropic virus type 1 (HTLV-1), Epstein–Barr virus (EBV) together with Kaposi's sarcoma-associated herpesvirus (KSHV) as oncogenic viruses that cause malignancy in human cells. Infections from the virus can cause cancer through direct cell attack of transformed cells yet the virus also serves as an indirect cancer trigger by creating persistent inflammation and suppress immune responses. The predisposition to cancer induced by human immunodeficiency virus type 1 (HIV-1) predominantly stems from immunodeficiency. Retroviruses harbor oncogenes originating from cellular genes that regulate mitogenic signaling and proliferation, whereas DNA tumor viruses encode oncoproteins that facilitate cellular transformation. To establish persistent infections, viruses have evolved sophisticated mechanisms to evade host immune surveillance and antiviral defenses. Furthermore, they can serve as cofactors, amplifying the oncogenic potential of other pathogens. However, no conclusive evidence currently supports the notion that viruses possess the pathogenic capacity to induce OC (Table 2) (33, 40, 41). For instance, Uterine and ovarian malignancies collectively constitute approximately 4% of newly diagnosed cancers in women. Although ovarian cancer is relatively less prevalent, it imposes a substantial mortality burden, with an age-standardized death rate of 3.8%. Notably, its prognosis remains dismal, with survival rates frequently falling below 50%, particularly when juxtaposed with other gynecological malignancies. Research focusing on ovarian and uterine neoplasms in women living with HIV remains scarce. However, a large-scale longitudinal study encompassing 85,268 women over 665,987 person-years observed a markedly lower incidence of uterine cancer compared to the general population, with only 31 reported cases (Standardized Incidence Ratio (SIR) 0.57; 95% Confidence Interval (CI) 0.39–0.81). Stratification based on menopausal status revealed an SIR of 0.86 (95% CI 0.54–1.32) in premenopausal women (<50 years) and a significantly lower SIR of 0.33 (95% CI 0.4–1.68) in postmenopausal women (>50 years). Within the same cohort, only 42 cases of ovarian cancer were identified (SIR 1.05; 95% CI 0.75–1.42). Regarding immunological status, no significant correlation was observed between the incidences of uterine or OC and factors such as AIDS diagnosis or CD4 count. However, infertility and impaired ovarian function are more prevalent among HIV-positive women compared to their HIV-negative counterparts, raising uncertainties about the potential impact of HIV on OC pathogenesis. Mortality data specific to ovarian and uterine cancers in HIV-positive populations remain scarce, likely due to the rarity of these malignancies. One Italian study reported that uterine cancer accounted for 4% of cancer-related deaths between 2006 and 2011. Furthermore, among women diagnosed with both AIDS and uterine cancer, the standardized mortality ratio was markedly elevated at 52.5 (95% CI 14.3–134.5) compared to non-AIDS counterparts within the same study (42, 43, 44). The review has set its purpose to combine available studies about HIV infection and ovarian cancer incidence along

with their underlying immune-pathological connections. A critical evaluation of epidemiological findings along with molecular mechanisms and clinical outcomes allows us to determine the impact of HIV-related immune dysfunction combined with persistent inflammation and prolonged antiretroviral treatment on ovarian cancer formation. This review evaluates research limitations in studying ovarian cancer diagnosis and treatment options for HIV-positive women before suggesting new areas for future scientific work. Our extensive evaluation aims to gener-

Table 1. Performance of selected serum biomarkers in differentiating benign adnexal masses from epithelial ovarian malignancy (45, 46, 47, 48, 49, 50)

	Benign		Type I EOC						Type II EOC					
	Median	**Cutoff value (75 percentile)**	**Median**	***p* value[a]**	**ROC AUC**	**Sensitivity[b] (%)**	**PPV (%)**	**NPV (%)**	**Median**	***p* value[a]**	**ROC AUC**	**Sensitivity[b] (%)**	**PPV (%)**	**NPV (%)**
CA125 (U/mL)														
Total	21.9	57.0	61.2	<0.001	0.76	51.5	34.0	86.0	567.2	<0.001	0.92	92.1	51.5	97.0
Pre-M	23.3	62.1	145.6	0.001	0.77	56.3	28.1	90.8	383.4	<0.001	0.94	92.9	36.1	98.6
Post-M	11.3	31.5	56.8	<0.001	0.81	64.7	52.4	82.9	701.9	<0.001	0.92	95.8	69.7	96.7
Early stage			42.0	0.002	0.70	39.1	21.4	87.5	186.2	0.001	0.81	72.7	19.5	97.0
Late stage			179.6	<0.001	0.88	80.0	19.5	98.0	721.7	<0.001	0.96	100.0	45.0	100.0
HE4 (pmol/L)														
Total	40.8	48.5	65.8	<0.001	0.82	78.8	44.1	93.3	310.9	<0.001	0.95	92.1	51.5	97.0
Pre-M	39.2	44.0	63.5	<0.001	0.84	81.3	36.1	95.8	135.4	<0.001	0.99	100.0	37.8	100.0
Post-M	48.4	63.3	96.8	0.003	0.75	58.8	50.0	80.6	502.1	<0.001	0.91	87.5	67.7	90.6
Early stage			55.6	<0.001	0.75	69.6	32.7	93.3	92.6	<0.001	0.87	72.7	19.5	97.0
Late stage			171.8	<0.001	0.99	100.0	23.3	100.0	478.1	<0.001	0.99	100.0	45.0	100.0
ROMA (%)														
Total	5.6 %	8.8 %	24.8 %	<0.001	0.85	84.8	45.9	95.1	92.4 %	<0.001	0.96	97.4	52.9	99.0
Pre-M	4.4 %	6.0 %	12.8 %	<0.001	0.84	75.0	34.3	94.5	61.7 %	<0.001	0.99	100.0	37.8	100.0
Post-M	11.0 %	19.6 %	40.1 %	<0.001	0.83	70.6	54.5	85.3	98.3 %	<0.001	0.93	91.7	68.8	93.5
Early stage			13.5 %	<0.001	0.80	78.3	35.3	95.1	42.0 %	<0.001	0.92	90.9	23.3	99.0
Late stage			61.8 %	<0.001	0.98	100.0	23.3	100.0	97.8 %	<0.001	0.98	100.0	45.0	100.0

Pre-M premenopausal, *Post-M* postmenopausal. [a]The *p* value was calculated as a statistical difference compared to benign diseases by Mann–Whitney *U* test. [b]The sensitivity was calculated at 75 % specificity of patients with benign diseases.

ate important findings which healthcare policymakers and those implementing preventive measures can use when developing strategies to reduce cancer vulnerability among this groups of patients.

In interpreting the literature on viruses in ovarian cancer, it is important to distinguish between several levels of evidence. First, viral presence refers to the detection of viral DNA, RNA, or protein in tumor tissue. Second, viral association refers to studies showing that viral markers are reported more frequently in ovarian tumors than in comparison tissues or are observed repeatedly across studies. Third, mechanistic plausibility refers to biologically credible pathways through which viruses might contribute to carcinogenesis, such as chronic inflammation, immune modulation, or interference with host signaling pathways. Finally, proven etiologic role requires much stronger evidence and cannot be inferred from detection alone. Therefore, the detection of viral material in ovarian tumor specimens should not be

Table 2. Studies reporting detection of viral markers in ovarian tumor samples (33, 51, 52, 53)

Histology of Tumors [a]	Prevalence; n (%)	Virus	Detection Method	Year
Epithelial ovarian adenocarcinoma, Epithelial ovarian tumor of low malignant potential, Epithelial ovarian adenoma	0/18 (0)	HPV6, 16, 18, 31, 35	Southern hybridization	1989
		HPV6, 11	PCR	
Serous OC	1/7 (14.28)	HPV16, 18	PCR (*E6* gene), Southern hybridization	1992
Mucinous OC	1/3 (33.3)			
Mixed (serous+mucinous OC)	1/1 (100)	HPV18		
Serous, Endometrioid, Mixed Undifferentiated, Clear cell, Malignant mixed Mullerian tumor with heterologous elements	0/28	HPV16, 18	PCR (*L1* and *E6* genes), dot blot	1995
Serous, Mucinous, Endometrioid, Clear cell, Brenner, Mixed epithelial, Unclassified epithelial	0/98	LR-HPV types (6, 11, 42, 44, 51, 53, 54, 55, 67, 68, 70) and HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56, 58, 66)	PCR (*L1* gene), ISH	1999
EOC	26/50 (52) 18/50 (36)	HPV16	ISH (*E6* gene) IHC (E6)	2003
Malignant ovarian tumor	15/40 (37.5)	Not specified	ISH, IHC	2005
Benign ovarian tumor	9/32 (28.1)			
Serous cystadenocarcinoma	8/76 (10.5)	HPV16, 33	PCR (*L1* gene); DNA sequencing	2007
Epithelial ovarian neoplasms	3/71 (4.2)	Not specified	PCR (*L1* gene)	2008
Serous adenocarcinoma	3/12 (25)	HPV6	Nested PCR (*E6* and *E7* genes)	2012
Mucinous adenocarcinoma	0/6 (0)			
Endometrioid adenocarcinoma	3/6 (50)			
Borderline serous OC	6/6 (100)			
Serous OC	2/35 (5.7)	HPV16	PCR (*L1* gene); DNA sequencing	2012
Mucinous OC	1/2 (50)			

Table 2. Studies reporting detection of viral markers in ovarian tumor samples (33, 51, 52, 53)

Endometrioid carcinoma	1/7 (14.28)			
Ovarian carcinoma	42/100 (42)	HPV16, 18, 45	Nested PCR (*L1* gene; DNA sequencing	2013
Non-cancerous tissue surrounding tumor	8/100 (8)	HPV6, 11		
EOC	2/20 (10) 2/20 (10) 4/20 (20)	HPV16 HPV18 HPV16/18	PCR (*E6* gene)	2014
Serous, Endometrioid, Mucinous, Clear-cell	1/191 (0.52)	HPV18	qRT-PCR (*E6/E7* genes)	2016
EOC	5/100 (5) 4/100 (4) 1/100 (1)	HPV16 HPV18 HPV33	Nested PCR (*L1* gene); DNA sequencing	2017
EOC	40/99 (40.4)	HPV2, 4, 5, 6b, 7, 10, 16, 18, 32, 48, 49, 50, 60, 54, 92, 96, 101, 128, 129, 131, 132	Microarray-based method, PathoChip Array	2017
Non-cancerous tissue surrounding tumor	20/20 (100)	HPV41, 88, 53, 103		
EOC	19/27 (70.4) 2/27 (7.4) 1/27 (3.7)	HPV16 HPV6 HPV45	Nested PCR (*E6* gene); DNA sequencing	2019
Metastatic ovarian tumors	4/ 4 (100)	HPV16		
Benign ovarian tumors	2/8 (25)			
Serous adenocarcinoma	6/12 (50)	CMV	Nested PCR (*UL55* gene)	2012
Mucinous adenocarcinoma	3/6 (50)			
Endometrioid adenocarcinoma	3/6 (50)			
Borderline serous OC	3/6 (50)			
Serous adenocarcinoma and other histotypes	34/45 (75.5) 11/42 (26.2)	CMV (IE) CMV (pp65)	IHC (IE and pp65)	2018
Benign ovarian cystadenoma	20/30 (67) 4/29 (14)	CMV (IE) CMV (pp65)		
HGSOC with prechemotherapy	8/10 (80)	CMV (IE)	IHC (IE and pp65), ISH (DNA ß2.7)	2018
HGSOC with neoadjuvant chemotherapy	4/10 (40) 3/3 (100) 4/9 (44) 5/8 (62.5) 5/5 (100)	CMV (pp65) CMV (DNA) CMV (IE) CMV (pp65) CMV (DNA)		
EOC Metastatic ovarian tumors Benign ovarian tumors	19/27 (70.4) 4/4 (100) 0/8 (0)	CMV	Nested-PCR (*US28* gene), DNA sequencing	2019
Serous, mucinous, and endometrioid adenocarcinomas, clear–cell carcinomas	1/191 (0.5)	CMV	qRT-PCR, DNA sequencing	2019
Ovarian serous cystadenocarcinoma	0/419 (0)	EBV	RNA-Seq	2013
Serous OC	38/487 (7.8)	EBV	miRNA expression, qRT-PCR	2014

Table 2. Studies reporting detection of viral markers in ovarian tumor samples (33, 51, 52, 53)

EOC	0/27 (0)	EBV	qRT-PCR, nested PCR	2019
Serous, mucinous, and endometrioid adenocarcinomas, clear–cell carcinomas	10/191 (5.2)	EBV	qRT-PCR, DNA sequencing, ISH	2019

[a] Histology of tumors as originally described by cited authors; n, number of cases with the virus genotype; HPV, human papillomavirus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; qRT-PCR, quantitative-real-time PCR; ISH, In situ hybridization; IHC, immunohistochemistry; OC, *ovarian cancer*; EOC, epithelial *ovarian cancer*; HGSOC, high grade serous ovarian carcinoma.
N**ote:** Detection of viral DNA, RNA, or protein in ovarian tumor tissue indicates viral presence only and does not by itself establish a causal or etiologic role in ovarian carcinogenesis.

interpreted as proof of causation, and the current literature on HPV, CMV, and EBV in ovarian cancer remains insufficient to establish a definitive etiologic role.

MATERIAL AND METHODS

This article was prepared as a narrative review of the published literature on gynecologic malignancies in women living with HIV, with particular attention to ovarian cancer. Relevant studies were identified through searches of major biomedical databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search included combinations of keywords such as "HIV," "women living with HIV," "ovarian cancer," "gynecologic malignancies," "HPV," "antiretroviral therapy," "immune dysfunction," and "clinical management." Studies published in English and considered relevant to the epidemiology, mechanisms, diagnosis, treatment, and outcomes of gynecologic malignancies in women with HIV were reviewed. Priority was given to systematic reviews, meta-analyses, cohort studies, clinical studies, and key mechanistic papers directly related to the topic. Articles considered unrelated to the scope of the review or lacking clear relevance to HIV-associated gynecologic malignancies were excluded. Because this work was conducted as a narrative review, a formal risk-of-bias assessment and PRISMA-style study flow diagram were not performed.

RESULTS AND DISCUSSION

Epidemiology of Ovarian Cancer in HIV-Positive Women

OC shows challenging health implications because patients are frequently diagnosed at advanced stages, when mortality risks are high despite the relative infrequency of the disease. Researchers have conducted multiple investigations to study the epidemiology of ovarian cancer in HIV-positive women because of its implications for incidence trends, disease presentation, and clinical outcomes.

Incidence: Scientific investigations have produced mixed findings regarding the incidence of ovarian malignancy among women with HIV. A comprehensive systematic review and meta-analysis reported a standardized incidence ratio (SIR) of 3.21 (95% confidence interval (CI): 2.29–4.13), suggesting a possible increased occurrence of OC in HIV-positive women relative to HIV-negative counterparts (1). Conversely, other investigations have reported no statistically significant variation in incidence rates. For instance, an extensive cohort study documented 42 occurrences of OC among HIV-positive women, resulting in a standardized incidence ratio (SIR) of 1.05 (95% confidence interval (CI): 0.75–1.42), thereby suggesting no appreciable elevation in risk (42). Taken together, these findings indicate that the association between HIV and OC incidence remains uncertain, as the available evidence is limited, heterogeneous, and largely observational. These inconsistencies underscore the imper-

ative for further investigative studies to clarify the epidemiology of OC within this demographic.

Presentation and Clinical Characteristics: Limited data are available regarding the clinical presentation of ovarian cancer in women living with HIV. In a multi-institutional cohort of 57 HIV-infected women with gynecologic cancers, 9 were diagnosed with ovarian cancer, and most of these cases (89%) were reported at advanced stage (II–IV). The median age at ovarian cancer diagnosis was 50 years, 77.8% of patients were Black, 77.8% were receiving combination antiretroviral therapy at the time of cancer diagnosis, and the median CD4 count was 403 cells/mm^3. Although these findings provide useful descriptive clinical observations, they are based on a very small ovarian cancer subgroup and should therefore be interpreted with caution. These data do not support broad conclusions regarding HIV-associated ovarian cancer biology, presentation, or management, and should instead be regarded as low-level, hypothesis-generating evidence (54, 55). The occurrence of ovarian cancer among women living with HIV remains incompletely defined, with available studies showing mixed results. Research indicates that women with *HIV* face an increased susceptibility to non-AIDS-defining malignancies, such as *ovarian cancer*. The rate of *ovarian cancer* seems to be marginally elevated in *HIV-positive* women when compared to the general population, possibly as a result of *HIV*-induced immunosuppression, which may alter tumor biology and accelerate its progression (56, 57, 58).

Pathophysiology of *Ovarian Cancer* in *HIV-positive Women*

Approximately 23% of adnexal tumors are linked to hereditary syndromes, predominantly hereditary breast and *OC* syndrome or Lynch syndrome, both of which are implicated in epithelial tumors. However, less common genetic conditions can give rise to non-epithelial ovarian tumors. Ovarian malignancies associated with BRCA gene germline mutations typically manifest as high-grade serous carcinomas of tubal origin, while those linked to Lynch syndrome are most often endometrioid or clear cell carcinomas. Familial predisposition can also lead to sex-cord tumors, including Sertoli-Leydig cell tumors in DICER syndrome and sex-cord tumors with annular tubules in Peutz-Jeghers syndrome (59, 60, 61, 21, 62, 63, 64, 65, 66, 67). And a study explores the association between DNA methylation (DNAm) in blood-derived leukocytes and epithelial ovarian cancer (EOC). The researchers analyzed blood-based DNAm in 336 EOC cases and 398 controls, concentrating on high-quality CpG loci that did not show any association with variations in white blood cell type distributions. Among 13,816 CpGs, no significant associations were found with survival, although eight CpGs exhibited survival associations at p < 10^−3, including methylation within a CpG island in the promoter region of GABRE. Conversely, 53 CpG methylation sites were significantly linked to EOC risk. The strongest association was found with the methylation probe cg04834572, located approximately 315 kb upstream of DUSP13. Other CpGs associated with the disease included those near or within HHIP, HDAC3, and SCR. DNA methylation's role in *ovarian cancer* is complex, with tumor tissue exhibiting distinct methylation patterns that correlate with histopathology. Blood-based DNAm patterns in relation to disease etiology and outcome have gained considerable attention, particularly in studying the variation in global methylation levels, the impact of exogenous exposures on leukocyte methylation, and the influence of inherited variants on leukocyte methylation (mQTL) (68, 69, 70, 71, 72, 73, 74, 75, 76).

Moreover, the findings revealed that ovarian epithelial tumor cells exhibited a simultaneous upregulation of miR-200, suppression of its four target genes (ZEB1, ZEB2, TGFβ1, and TGFβ2), and increased expression of downstream effector genes negatively modulated by these targets. Serous tubal intraepitheli-

al carcinoma (STIC) tumor cells demonstrated analogous expression patterns, though the observed effects did not achieve statistical significance due to limited sample sizes. Introduction of synthetic miR-200 precursors into normal ovarian surface epithelial (OSE) and fallopian tube epithelial (FTE) cells corroborated a reduction in target gene expression alongside elevated levels of effector genes such as CDH1, CRB3, and EpCAM in both cell types. Notably, only FTE cells displayed a specific induction of CA125 following miR-200 precursor transfection. The activation of the miR-200 pathway appears to be an early molecular event predisposing OSE and FTE cells to oncogenic transformations and histologic specialization. That high-grade serous ovarian carcinomas (HGSOC) are typically characterized by elevated CA125 levels, the observed induction of CA125 expression in FTE cells upon miR-200 precursor transfection aligns with the hypothesis that HGSOC originates in the distal fallopian tube epithelium (77, 78, 79, 47, 80, 81, 82, 83). And *OC* represents a prevalent gynecological malignancy characterized by an alarming mortality rate, rendering early diagnosis and therapeutic intervention exceptionally challenging. Cellular senescence, a fundamental biological phenomenon, exerts a pivotal influence on the initiation, progression, and therapeutic responsiveness of *ovarian cancer*, including its reaction to chemotherapy and biotherapy. Nevertheless, the intricate molecular mechanisms governing senescence in *ovarian cancer* cells remain largely enigmatic. Sphingosine-1-phosphate (S1P), a crucial bioactive lipid, significantly contributes to oncogenesis and is synthesized via the phosphorylation of sphingosine kinase 1/2 (SPHK1/2) at the cellular membrane, subsequently engaging with sphingosine-1-phosphate receptors (S1PRs). Among these, S1PR1 is implicated in tumorigenesis, while the S1P/S1PR1/3 axis plays a regulatory role in angiogenic processes. However, the precise function of Yes-associated protein (YAP) in orchestrating cellular senescence within *OC* remains to be elucidated (84, 85, 86, 87, 88, 89, 90).

Clinical Manifestation and Diagnosis of *Ovarian Cancer* in *HIV-Positive* Women

Diagnosing ovarian cancer in women living with HIV may be challenging because overlapping clinical symptoms can delay recognition. The symptomatology shared by *HIV* infection and cancer can obscure early detection, potentially leading to delayed diagnoses. Additionally, the lower engagement of *HIV-positive* women in routine cancer screenings may result in diagnoses at more advanced stages of the disease (57, 90). And a 38-year-old female with early-stage ovarian mucinous carcinoma complicated by progressive bulbar paralysis (PBP) underwent a transabdominal right adnexal resection under regional anesthesia and epidural block. Following a one-month follow-up, her CA19-9 levels dropped to 14.50 IU/ml. This case underscores the necessity of a multidisciplinary approach in the management of patients with germline ovarian carcinomas (GOCs) accompanied by PBP (92, 51, 93, 94, 95).

A research analyzed 1,133 women diagnosed with invasive epithelial ovarian cancer (iEOC) in 2014 while the majority of participants were White (98%). It found that 2% had a maternal history of *ovarian cancer*, and 5% had a personal history of breast cancer. The median age of diagnosis was 66.8 years in the CD group and 68.7 years in the PC group. For high-grade serous carcinoma (HGSC), the median age of diagnosis was 67.0 years for the PC group and 69.0 years for the CD group. The study also examined symptoms reported by women in both groups. In the PC group, 47% of women reported symptoms, with abdominal discomfort being most common. When tested with the modified GSI and NSG, fewer symptomatic women in the PC group were identified compared to those in the CD group (27% vs. 61% by GSI and 31% vs. 64% by NSG). Notably, only 39% of women with early-stage disease and 51% with advanced-stage disease in the PC group were symptomatic, compared to 84% and 91%, respectively, in the CD group. Symptomatic women with HGSC commonly reported multiple symptoms, particularly abdominal ones, but the symptom profiles differed between the two groups (96, 20, 97, 98). And High-grade serous

ovarian carcinoma (HGSOC), recognized as the most fatal subtype of epithelial ovarian cancer (EOC), is frequently identified at an advanced stage. In women presenting with a detected pelvic mass, surgical intervention coupled with pathological evaluation remains the gold standard for EOC diagnosis. To enhance early detection, a liquid biopsy utilizing cell-free DNA methylation profiling has been innovatively designed for assessing the risk of early-stage HGSOC (99, 100, 101, 102). Alongside, HGSOC represents the most prevalent and lethal form of ovarian epithelial malignancy, accounting for approximately 70% of *ovarian cancer*-related fatalities. The precise cellular progenitor of HGSOC remains a subject of debate, with both the fallopian tube epithelium (FTE) and ovarian surface epithelium (OSE) proposed as potential origins. This study employing genetically engineered murine models and organoid systems evaluated the tumorigenic potential of FTE and OSE, demonstrating that both cell types exhibit identical oncogenic aberrations. The concurrent inactivation of the RB protein family alongside Tp53 mutation in *Pax8*$^{+}$ FTE precipitated the formation of serous tubal intraepithelial carcinoma (STIC), which rapidly disseminated to the ovarian surface. Introducing the same genetic alterations into *Lgr5*$^{+}$ OSE or OSE-derived organoids also resulted in metastatic HGSOC, albeit with prolonged latency and reduced penetrance. Transcriptomic analyses revealed distinct gene expression profiles between tumors originating from FTE and OSE, and comparative transcriptomics and genomics indicate that human HGSOC likely arises from both cellular lineages. These findings support a dualistic model of HGSOC pathogenesis and imply that the cellular origin may play a critical role in shaping therapeutic responsiveness (103, 104, 105, 106, 107, 108, 109, 110).

Additionally, *OC* represents a highly lethal gynecological malignancy in women, characterized by a poor prognosis primarily due to the absence of reliable early diagnostic markers. KAZN, a gene implicated in various biological processes during development, has been associated with aberrant cellular behaviors such as malignancy. This investigation assessed KAZN expression and methylation patterns as potential biomarkers (Table 3) for the early detection of *OC*. Data obtained from Gene Expression Omnibus (GEO) microarrays, The Cancer Genome Atlas (TCGA), and the Clinical Proteomic Tumor Analysis Consortium (CPTAC) were analyzed to explore the relationship between KAZN expression and clinical features of *OC*. The findings revealed that KAZN was upregulated in ovarian epithelial tumors and correlated with patient survival outcomes. The CpG site cg17657618 within KAZN exhibited a positive correlation with mRNA expression, with significant differential methylation observed between stage I/II and stage III/IV OC groups. Additionally, this study introduces a novel approach for distinguishing tumor and normal tissues in *OC* based on DNA methylation profiles within the KAZN gene body region (111, 112, 113, 114). A three-marker serum panel based on DNA methylation was developed using ultra-high coverage bisulfite sequencing in 151 women and subsequently validated in 250 women with diverse conditions, particularly those associated with elevated CA125 levels, such as endometriosis and other benign pelvic masses. This marker panel effectively distinguished high-grade serous *OC* patients from healthy women or those with benign pelvic masses, achieving a specificity of 90.7% and sensitivity of 41.4%. After chemotherapy, the levels of all three markers significantly decreased and accurately identified 78% of responders and 86% of non-responders. The study concluded that DNA methylation signatures in cell-free DNA hold promise for detecting *ovarian cancer* up to two years prior to diagnosis and could potentially inform personalized treatment strategies. Also, the use of innovative collection vials, which stabilize blood cells and minimize background DNA contamination in serum or plasma, may enhance the clinical application of liquid biopsy approaches (Figure 1) (115, 25, 79, 116, 117).

For instance, Medical personnel incorrectly diagnosed a 65-year-old woman who gave birth many times of having massive ascites based on her enlarged abdomen. Right giant

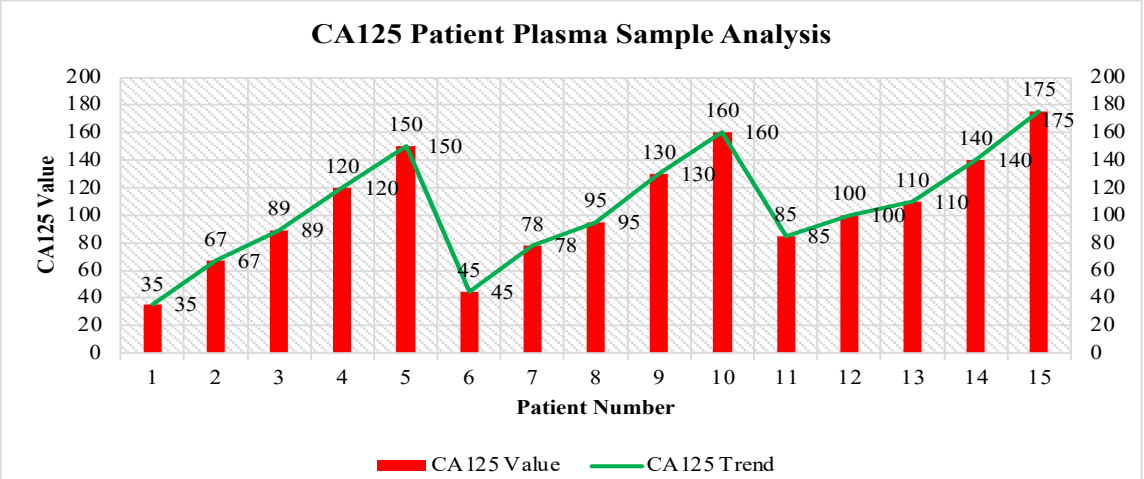

Figure 1. Evaluated plasma samples between 74 epithelial *ovarian cancer* patients and 86 healthy volunteers combined with 20 benign case patients through Cell-free Methylated DNA Immunoprecipitation Sequencing [cfMeDIP-seq] analysis to identify cancer and non-cancer sample classifications. Researchers performed preoperative blood processing after which they analyzed DNA methylation markers through machine learning to distinguish cancerous from non-cancerous tissue samples. The analysis of late-stage *ovarian cancer* through Area Under the Receiver Operating Characteristic Curve [AUROC] testing achieved high classification precision rates between 0.97–0.98 but early-stage detection yielded encouraging results between 0.86–0.96. The efficiency of models based on late-stage clinical data decreased in early-stage diagnosis while early-stage diagnostic markers yielded comparable performance for both early and late lesions. The discovery demonstrates that cfMeDIP-seq performs at an equivalent or better level than the Cancer Antigen 125 [CA125] protein marker for detecting latent *ovarian cancer* [123, 124, 125].

Table 3. Selected ovarian cancer biomarkers and their reported diagnostic or prognostic applications in the literature (126, 127, 128, 129, 35, 130, 131)

Test Name	Marker(s)	Modality	Potential Clinical Application(s)	Average Sens./Spec. (%)
N/A	CA125	Protein	Preoperative diagnostic, Prognostic (FDA cleared)	83.7/86.0
ROMA®	CA125, HE4, and Menopause Status	Protein	Preoperative diagnostic, Prognostic (FDA cleared)	85.3/80.9
CPH-I	CA125, HE4, and Age	Protein	Preoperative diagnostic, Prognostic	82.2/78.9
OVA1®	CA125, ApoA-1, TTR, TF, and B2M	Protein	Preoperative diagnostic, Prognostic (FDA cleared)	87.7/52.6
Overa®	CA125, ApoA-1, TF, HE4, and FSH	Protein	Preoperative diagnostic, Prognostic (FDA cleared)	91.1/67.6
N/A	CA125, CA 15-3, CA72-4, and MCSF	Protein	Diagnostic	69.5/98.0
PapSEEK	ctDNA mutations	Genetic	Diagnostic, Prognostic	63.0/99.9
N/A	*OPCML* hypermethylation	Epigenetic	Screening, Diagnostic, and Prognostic	90.1/91.8
N/A	*ZNF154* hypermethylation	Epigenetic	Diagnostic	67.6/93.5
CancerSEEK	ctDNA mutations and glycoproteins	Pan-cancer	Screening, Diagnostic, and Prognostic	96.0/99.0
N/A	miR-200(a/b/c) + miR-320 + miR-141, among others	MicroRNA	Diagnostic, Prognostic	85.3/96.0
N/A	VLDL, LDL, lysoPC, valine, alanine, and ceramides	Metabolite	Prognostic	78.9/93.2

CA125, cancer antigen 125; ApoA-1, apolipoprotein A1; TTR, transthyretin; TF, transferrin; B2M, beta-2-microglobulin; HE4, human epididymis protein 4; FSH, follicle stimulating hormone; CA72-4, cancer antigen 72-4; CA 15-3, cancer antigen 15-3; MCSF, macrophage colony stimulating factor; VLDL, very low-density lipids; LDL, low-density lipids; LysoPC, Lysophosphatidylcholines; ctDNA; circulating tumor DNA.
Note: Although several biomarkers have been investigated for early detection, these assays should not be interpreted as established screening tools for asymptomatic average-risk women. Rather, they are better viewed as diagnostic, triage, prognostic, or investigational approaches.

multiloculated ovarian cyst was identified through abdominal ultrasound scan. The surgical procedure called cystectomy completed without difficulty. Histopathology revealed mucinous cystadenoma. The medical example shows why professionals need to detect huge cystic ovarian tumors because these tumors sometimes appear as enormous ascites while leading physicians down incorrect diagnostic paths. The case demonstrates the necessity for quick identification and suitable treatment of highly unusual types of ovarian cysts (118, 119, 120, 121, 122).

Risk Factors and Comorbidities

Mechanisms Linking HIV to Increased Cancer Risk: - Explore the underlying biological mechanisms that elevate the risk of *ovarian cancer* in *HIV-positive* women. The persistent immune activation and immunosuppressive state induced by *HIV* may enhance vulnerability to a range of malignancies, including *ovarian cancer*. Factors associated with *HIV*, such as diminished CD4 counts and inadequate antiretroviral therapy (ART), may further amplify the risk of developing cancer (56). Horackova et al. (2024) conducted at Charles University in Prague revealed that patients diagnosed with early-onset OC at or before the age of 30 exhibit distinct characteristics compared to those with late-onset OC, particularly regarding uncertain germline cancer predisposition. The study determined that merely 6.9% of early-onset OC cases harbored a germline pathogenic variant (GPV) in high-penetrance genes associated with OC susceptibility, highlighting a potential divergence in genetic etiology (132, 133, 134).

HGSOC represents the most prevalent and lethal form of *ovarian cancer* in both Canada and the United States. Approximately 20-30% of these cases are linked to inherited pathogenic or likely pathogenic variants (PVs) in cancer susceptibility genes. Women carrying inherited BRCA1/2 PVs face an *ovarian cancer* risk ranging from 17-44%, while PVs in other *ovarian cancer*-related genes confer a 6-24% risk. Genetic testing is now a standard recommendation for all HGSOC diagnoses, irrespective of the patient's age or family history. Recently, the role of genetic testing in HGSOC has evolved beyond identifying hereditary cancer syndromes; it is also pivotal in identifying patients who could benefit from targeted therapeutic approaches. For instance, poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated superior outcomes in the treatment of HGSOC, particularly in those with BRCA1/2-associated cancers. Implementing routine reflex testing for BRCA1/2 mutations in all newly diagnosed HGSOC cases could enhance treatment precision and streamline the genetic testing process (Figure 2) (135, 136, 137, 138, 139, 60, 140, 141, 142). According to Öfverholm et al. (2023), "the overall diagnostic yield was 16.6%, with BRCA1/2 variants found in 8.9% of women. In addition to BRCA1/2, 11 other genes increased diagnostic yield by 7.7%" (143, 144, 145). And Germline mutations in the BRIP1 gene have been linked to a moderate increased risk for *OC*, though its role in the pathogenesis of breast cancer (BC) remains debated. A study was conducted to evaluate the impact of deleterious BRIP1 germline mutations on susceptibility to both BC and *OC*. The findings revealed that BRIP1 loss-of-function (LoF) mutations are associated with a significantly elevated risk of *OC* in familial index patients, particularly in those with late-onset *OC*. No substantial correlation between BRIP1 LoF mutations and familial BC was identified. Furthermore, in familial BC patients without a family history of *OC*, no significant association was found. Among 1,027 familial BC index patients with a history of *OC*, the prevalence of BRIP1 mutations was notably higher than in controls. The higher mutation frequency observed in this group was attributed to the presence of *OC* within these families, as indicated by the negative correlation between BRIP1 LoF mutations and familial BC in the absence of *OC* history. Moreover, rare missense variants predicted to be damaging were significantly more common in *OC* patients compared to BC patients, though no such association was observed for BC (146, 147, 148, 149, 150, 151, 152, 153).

Mechanisms Linking HIV to Increased Ovarian Cancer Risk

Although *HIV* infection has been correlated with an augmented susceptibility to certain malignancies, the precise biological mechanisms underpinning its potential linkage to an increased risk of *ovarian cancer* remain inadequately elucidated. Nevertheless, multiple plausible pathways may play a contributory role in this association:

1. *Immunosuppression: HIV*-mediated deterioration of immune function compromises the body's capacity for oncogenic surveillance and eradication of neoplastic cells, thereby potentially predisposing individuals to an elevated risk of malignancy (154).
2. *Chronic inflammation:* Sustained immune activation and prolonged inflammatory responses in *HIV-positive* individuals may foster a microenvironment that facilitates oncogenesis, potentially contributing to the pathogenesis of *OC* (155).
3. *Carcinogenic Viral Co-infections:* Individuals with HIV exhibit an increased susceptibility to oncogenic viral infections, such as human papillomavirus (HPV), which are established contributors to several malignancies, particularly cervical, anal, and other squamous cancers; however, this should not be interpreted as evidence of a causal role in ovarian cancer (56).
4. *Direct Impact of HIV Proteins:* Viral proteins such as gp120 and Tat have been implicated in oxidative stress and altered cellular signaling in experimental systems; however, their relevance to ovarian car-

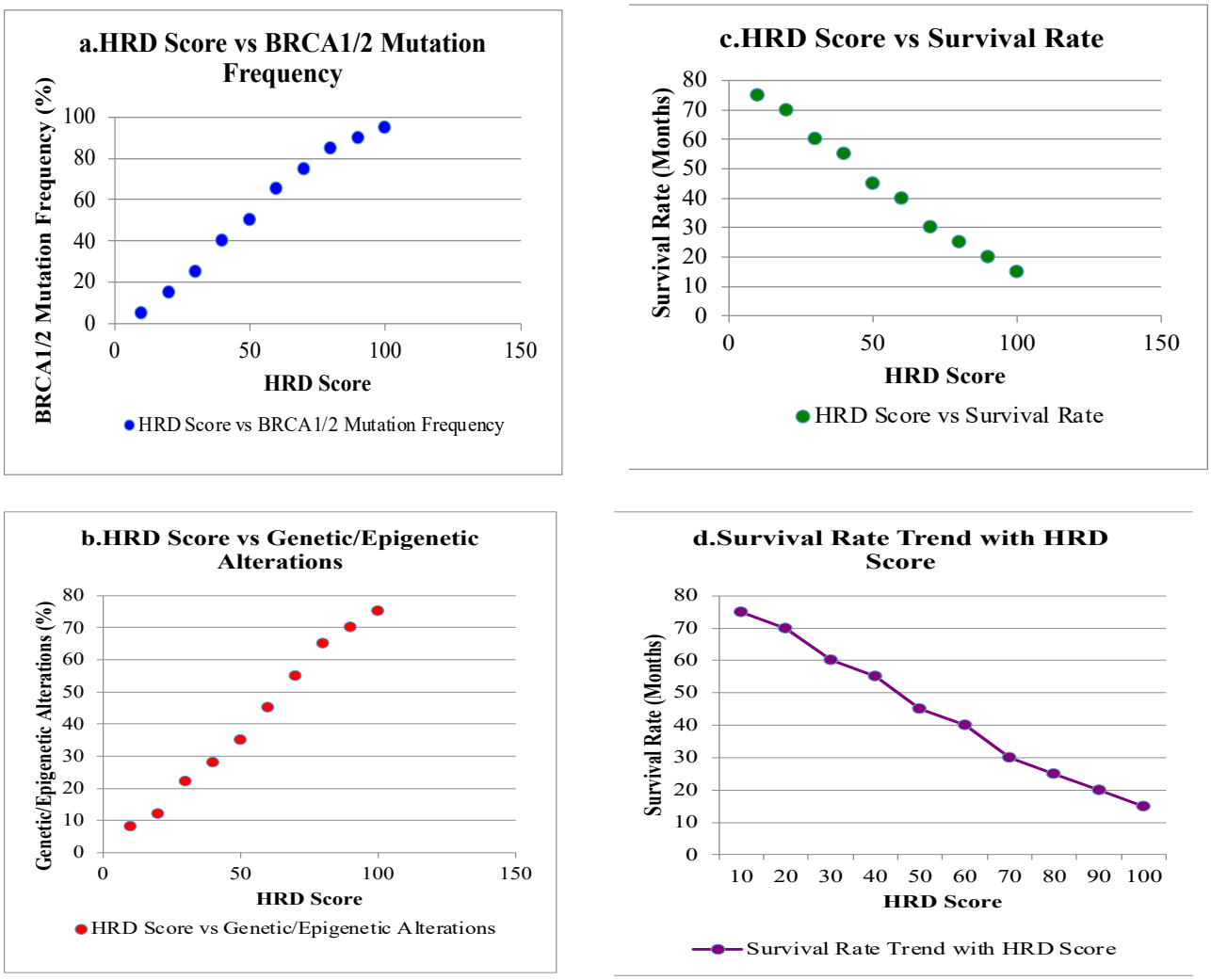

Figure 2. The analysis highlights Homologous Recombination Deficiency [HRD] Score as a key biomarker in cancer prognosis and treatment. Higher HRD scores correlate with increased Breast Cancer Gene 1/2 (BRCA1/2) mutations, genetic instability, and lower survival rates, emphasizing its dual role-sensitizing tumors to therapy while driving malignancy. Integrating HRD scoring into clinical strategies is crucial for personalized treatment and improved outcomes [160, 161, 162].

cinogenesis remains hypothetical, and an ovarian-specific oncogenic mechanism has not been established (155).

Although these pathways may be biologically plausible in a general oncogenic context, current evidence does not establish HPV or HIV proteins as ovarian-specific drivers of carcinogenesis. The persistent immune activation and immunosuppressive state induced by *HIV* may enhance vulnerability to a range of malignancies, including *ovarian cancer*. Factors associated with *HIV*, such as diminished CD4 counts and inadequate antiretroviral therapy (ART), may further amplify the risk of developing cancer (156, 157, 158, 159).

Impact of Antiretroviral Therapy on *Ovarian Cancer*

Impact of ART on Ovarian Cancer Risk: The influence of antiretroviral therapy (ART) on the risk propensity for *ovarian cancer*. While ART has markedly enhanced the life expectancy of individuals living with *HIV*, certain studies propose that the long-term use of ART may engage in intricate interactions with cancer pathogenesis. For example, while ART may effectively suppress HIV viral load, it may not entirely reduce the risks associated with HPV-related cancers; however, such evidence should not be extrapolated to imply an established effect on ovarian cancer incidence (57, 163, 164, 165, 166).

The advent of antiretroviral therapy (ART) in 1995 substantially altered the morbidity and mortality landscape of the *HIV*-infected population, thereby influencing the trajectory of cancer development. A retrospective observational study conducted at the Moffitt Cancer Center from 2000 to 2010 involving 279 *HIV-positive* patients revealed that 33.5% of male patients presented with AIDS-defining cancers, with AIDS-related non-Hodgkin lymphoma (NHL) being the most prevalent. In contrast, 23% of males were diagnosed with non-AIDS-defining cancers (NADC), with anal cancer emerging as the most common. Among women, AIDS-related NHL was also the most frequent malignancy, affecting 19.5% of the cohort. Among white patients, the prevalence of AIDS-defining cancers was 34%, with NHL accounting for 21%, Kaposi's sarcoma (KS) 13%, and invasive cervical cancer (ICC) 1.5%. Non-AIDS-related NHL was the second most common cancer, followed closely by breast cancer and anal cancer, each with a prevalence of approximately 6.5%. The rising incidence of certain NADC is anticipated, as the *HIV* population experiences prolonged survival with chronic exposure to oncogenic viruses, such as HPV, HBV, and EBV, which contribute to viral replication and subsequent cancer development (167, 168, 169, 170).

Treatment Approaches for *Ovarian Cancer* in *HIV-positive Women*

Treatment and Outcomes: Review the treatment options for *OC* in *HIV-positive* women and the outcomes of these treatments. Given that many clinical trials exclude *HIV-positive* women, there is limited data on the effectiveness of various treatment regimens. This section should explore the clinical management of *ovarian cancer* in this population and the impact of HIV on treatment response and survival rates (57, 171).

OC ranks as the third most lethal malignancy among women, with chemotherapy serving as the primary therapeutic modality. Platinum-based agents, notably cisplatin, remain the cornerstone of treatment for *OC* patients. Nevertheless, resistance to cisplatin often culminates in therapeutic inefficacy and tumor relapse. This resistance is attributed to multiple mechanisms, including reduced intracellular accumulation of cisplatin, amplified drug efflux, modifications in DNA repair pathways, and the activation of signaling networks that impede apoptotic processes (172). Emerging research indicates a connection between chemotherapy resistance and ferroptosis, an iron-dependent form of cell death. Ferroptosis is triggered by the excessive buildup of lipid peroxides, which can potentially enhance chemosensitivity by amplifying oxidative stress. Despite the initial success of platinum-based therapies, the emergence of resistance presents a formidable challenge, undermining long-term treatment efficacy (173, 174, 175,

176, 177, 178, 179). Deficiency in homologous recombination repair (HRD) is a prevalent characteristic in high-grade serous carcinomas of the ovary, fallopian tube, and peritoneum (HGSC) and is associated with heightened susceptibility to PARP inhibitor (PARPi) therapy. While HRD testing holds potential for refining the use of PARPi in HGSC, its clinical implementation remains a subject of debate (180, 181, 182, 162, 183).

Furthermore; the expression of Forkhead Box M1 (FOXM1) is strongly correlated with chemotherapy resistance and poor prognosis in patients with non-serous epithelial ovarian cancer (EOC). FOXM1, an oncogene that is aberrantly upregulated in various solid malignancies, including serous EOC, has yet to be fully elucidated in the context of non-serous EOCs. It investigated the expression of FOXM1 and its association with prognosis across the three primary subtypes of EOC, as well as its involvement in tumorigenesis and chemoresistance through in vitro analysis (184, 185, 186).

OC encompasses a diverse spectrum of neoplastic disorders, primarily exhibiting loco-regional propagation within the ovary and adjacent pelvic structures. Over 90% of malignant ovarian neoplasms originate from epithelial cells, with high-grade serous ovarian carcinoma (HGSOC) representing the most prevalent and aggressive subtype. Given its hallmark features, including homologous recombination deficiency and ubiquitous TP53 mutations, HGSOC serves as the principal model guiding treatment protocols for epithelial ovarian cancer (EOC). Among emerging therapeutic modalities, gene therapy-particularly virotherapy-has garnered significant interest, yielding promising preclinical outcomes (Figure 3). Adenoviruses (Ad) remain the most extensively characterized vectors for virotherapy, owing to their high genomic payload capacity, broad tropism for both proliferating and quiescent cells, non-integrative nature, and relatively

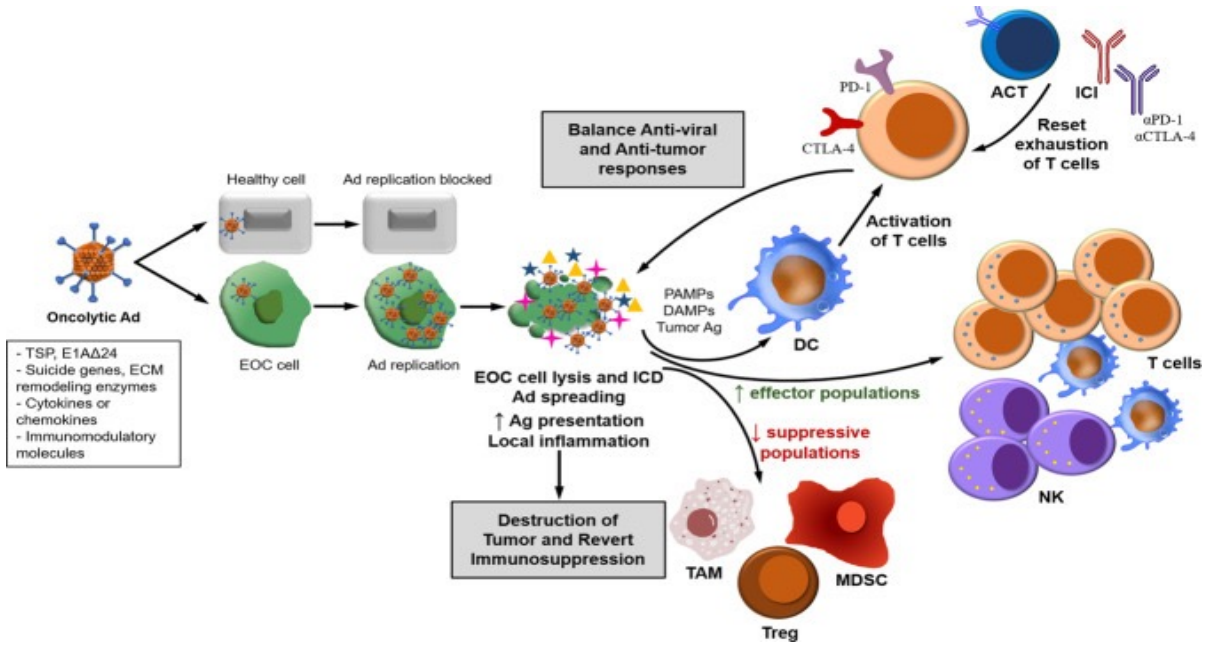

Figure 3. *Challenges in Adenoviral Vector Delivery:* Introduction of adenoviral vectors into the complex peritoneal biological environment creates major difficulties for efficient tumor infection. Suboptimal viral distribution combined with accelerated aggregation and clearance as well as cytotoxic effects stand as barriers to successful delivery. The therapeutic benefits of uniform treatment and EOC cell infection become obstructed when these limitations occur. The execution of genetic and chemical and physical vector modifications serves to make the delivery more specific while reducing unwanted side effects in IP applications. Performance of Ad vectors depends on the interaction of three primary anatomical structures together with two immunological elements which consist of the liver (L), omentum (O), mesentery (M), tumor (T) along with dendritic cells (DC) and natural killer (NK) cells [187].

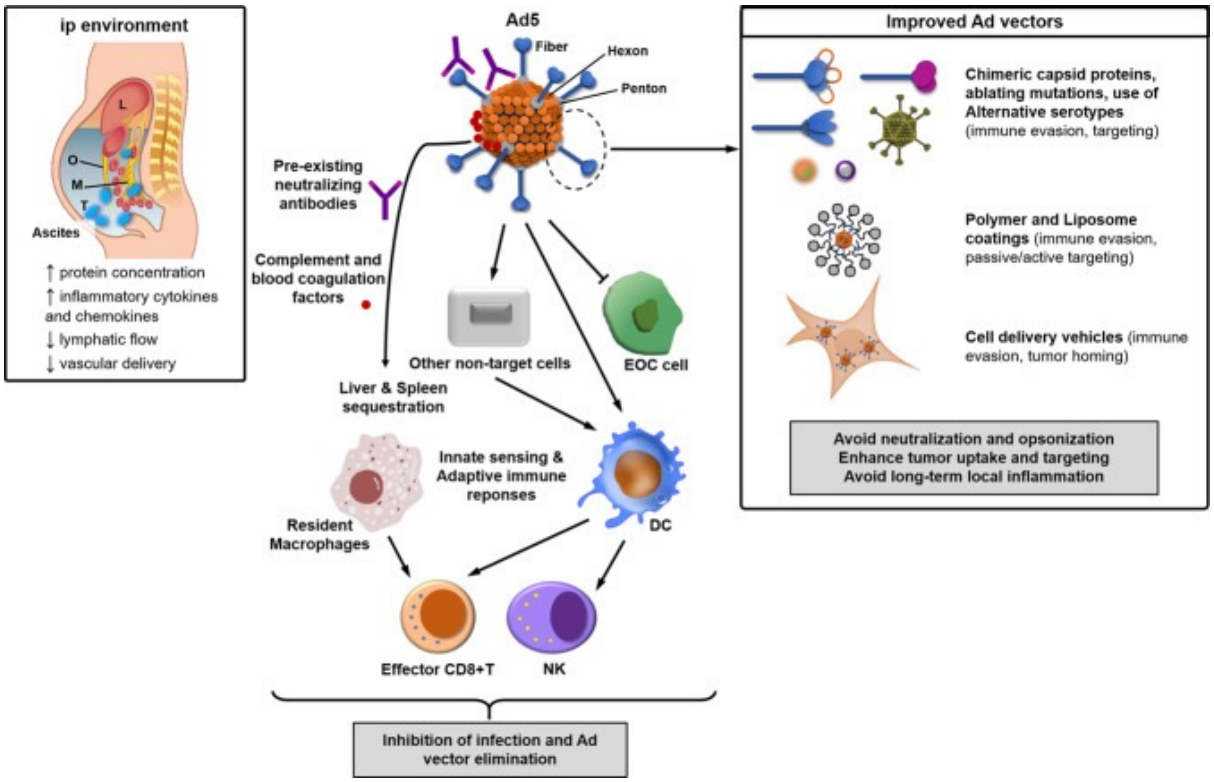

Figure 4. Oncolytic adenoviruses (Ads) selectively replicate in *ovarian cancer* cells, inducing oncolysis and enhancing immune activation. They trigger the release of tumor antigens, boost antiviral responses, and recruit immune cells to overcome immunosuppression. When combined with immunotherapy, they help prevent T cell exhaustion and enhance anti-tumor immunity [187, 193].

mild pathogenicity in human hosts (Figure 4) (187, 188, 189, 190, 191, 192).

Management Strategy for ART-Naive Individuals Living with HIV and Cancer

ART Initiation and Considerations: Current HIV guidelines recommend antiretroviral therapy (ART) for all people living with HIV and advise initiation immediately, or as soon as possible after diagnosis, regardless of CD4 count. In patients with cancer, timely ART initiation is important because it improves immune recovery, reduces HIV-related morbidity, and supports safer oncologic management. ART selection in this setting should be individualized, with particular attention to potential drug–drug interactions between antiretroviral agents and anticancer therapies, as well as antiemetics, corticosteroids, anticoagulants, and other supportive medications (225)

Recommended Regimens: In adults, current preferred initial regimens are generally based on an integrase strand transfer inhibitor (INSTI) combined with nucleoside reverse transcriptase inhibitors (NRTIs). In selected clinical situations, simplified two-drug regimens may also be appropriate. For patients undergoing cancer treatment, INSTI-based regimens are often favored because they are generally better tolerated and have a lower risk of clinically significant drug–drug interactions than boosted regimens. Regimen choice should therefore be made in coordination with HIV and oncology specialists and tailored to organ function, concomitant medications, and treatment goals (225)

Overcoming Barriers to ART: Barriers to ART initiation in patients with cancer may include delayed coordination between specialties, concerns about toxicity, adherence challenges, and the complexity of multimodal treatment. These barriers should be addressed through multidisciplinary care, early treatment planning, and close follow-up to ensure that HIV management is integrated with cancer therapy (225).

Urgent ART Initiation: Although ART is recommended for all people with HIV, prompt ini-

tiation is especially important in patients with advanced immunosuppression, AIDS-defining conditions, or malignancy-related risks of further immune compromise. In such cases, careful coordination is needed to balance rapid ART initiation with the timing of chemotherapy and supportive care (194, 195, 225).

Furthermore, the healthcare sector faces two main public health problems in sub-Saharan Africa due to high frequencies of HIV infection and cervical premalignant lesions in HIV-positive females reaching 20% and 9% respectively. Cervical cancer (CC) is classified as an AIDS-defining malignancy, with a global incidence ranging from 43.3 to 69.8 per 100,000 women. Persistent HPV infection compromises the host's immune surveillance, facilitating the progression from premalignant cervical lesions to invasive carcinoma. The 2015 World Health Organization (WHO) guidelines expanded antiretroviral therapy (ART) eligibility to all HIV-positive individuals, thereby improving life expectancy but concurrently elevating the risk of developing other AIDS-related malignancies. CC incidence in Africa exhibits significant regional variability, with the underlying pathophysiological mechanisms, particularly in HIV-positive women, remaining incompletely elucidated. Disparities in the diagnostic performance of screening modalities across different geographic regions further complicate the establishment of an optimal screening strategy. While Pap smear testing demonstrates high diagnostic accuracy for cervical lesions, its implementation in low- and middle-income countries (LMICs) is constrained by financial, infrastructural, and human resource limitations. Consequently, reassessment of traditional cytology-based screening approaches is warranted to enhance coverage among women at elevated risk for invasive cervical carcinoma. Visual inspection with acetic acid (VIA) has been recommended

Table 4. The diagnostic accuracy of VIA, as measured by sensitivity and specificity, varies among *HIV-positive* women across diverse studies

References	Country	N	HIV status	Reference test	Sensitivity (%)	Specificity (%)
Akinwuntwan et al	Nigeria	205	HIV-positive	Histology (CIN2+)	76	83
Mabeya et al	Kenya	150	HIV-positive	Histology (CIN2+)	70	51
Kuhn et al	South Africa	956	Mixed	Histology (CIN2+)	64	74
Fihrnaber et al	South Africa	1,202	HIV-positive	Histology (CIN2+)	65	69
Dartell et al	Tanzania	3,603	Mixed	Cytology (HSIL+)	50	91
Chung et al	Kenya	500	HIV-positive	Histology (CIN2+)	63	66
Chibwesha et al	Zambia	200	HIV-positive	Histology (CIN2+)	48	92

Table 5. The diagnostic accuracy of VIA, as measured by sensitivity and specificity, varies among *HIV-positive* women across diverse studies

References	Country	N	HIV status	Test used	Reference test	Sensitivity (%)	Specificity (%)
Fihrnaber et al	South Africa	1,202	HIV-positive	HC2 (Qiagen)	Histology (CIN2+)	92	51
Kuhn et al	South Africa	956	Mixed	HC2 (Qiagen)	Histology (CIN2+)	94	64.4
Chibwesha et al	Zambia	200	HIV-positive	GeneXpert	Histology (CIN2+)	88	60
Dartell et al	Tanzania	3,603	Mixed	HC2 (Digene)	Cytology (HSIL+)	94.2	82.8
Chung et al	Kenya	500	HIV-positive	Enzyme immunoassay	Histology (CIN2+)	83.6	55.7
Adamson et al	South Africa	308	HIV-positive	Aptima HPV mRNA assay on self-collected samples	HPV mRNA assay on clinician-collected samples	77.4	77.7
Segondy et al	South Africa	943	HIV-positive	*care*HPV and INNO-LiPA	Histology (CIN2+)	93.3 (*care*HPV) 96.7 (INNO-LiPA)	57.9 (*care*HPV) 32.0 (INNO-LiPA)
Ngou et al	South Africa; Burkina Faso	160	HIV-positive	HC2 and INNO-LiPA	Histology (CIN2+)	88.8 (HC2) 92.5 (INNO-LiPA)	55.2 32.1

Abbreviations: CIN2+, cervical intraepithelial neoplasia grade 2 or worse; HC2, Hybrid Capture 2; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSIL+, high-grade squamous intraepithelial lesion, VIA, visual inspection with acetic acid.

as a cost-effective alternative for cervical cancer screening in resource-limited settings (Table 4, 5) (196, 197, 198, 199).

Additionally, a retrospective cohort study examining HIV-positive women diagnosed with gynecologic malignancies revealed that the majority did not receive care adhering to National Comprehensive Cancer Network (NCCN) guidelines, resulting in poorer survival outcomes compared to those who did. The study analyzed data from 57 women diagnosed with vulvar, cervical, ovarian, and endometrial cancers between 2000 and 2015, with a median interval of 8.5 years between HIV diagnosis and cancer onset. Notably, 88% of the cohort comprised Black women. The findings underscore the necessity of addressing treatment-related toxicities and patient-specific barriers to oncologic care in this population. The widespread implementation of combination antiretroviral therapy (cART) has significantly decreased mortality among HIV-positive individuals, leading to its universal recommendation. As life expectancy for these individuals improves, the demand for oncologic treatment, particularly for gynecologic malignancies, will continue to rise. Given this demographic shift, it is imperative to assess treatment modalities and clinical outcomes among HIV-positive women with gynecologic cancers. This retrospective cohort study aimed to evaluate adherence to NCCN guidelines and identify factors contributing to deviations from guideline-based oncologic

Table 6. Demographic and Clinical Profiles of *HIV-Positive* Women with Gynecologic Cancer

	Vulvar N=15 (26.3%)	Cervical N=26 (45.6%)	Ovary N=9 (15.8%)	Uterine N=7 (12.3%)	Total N=57
Stage I	8 (53.4%)	16 (61.5%)	1 (11.1%)	5 (71.4%)	30 (52.6%)
Stage II–IV	7 (46.6%)	10 (38.5%)	8 (88.9%)	2 (28.6%)	27 (47.4%)
Demographics	**Median (IQR)**				
Age	47 (38–50)	45 (35–46)	50 (44–51)	53 (44–68)	46 (38–50)
Body Mass Index	25.4 (23.1–30.2)	27.1 (21.5–28.9)	30.7 (25.2–33.6)	34.7 (29.6–38.2)	27.6 (23.1–32.0)
Race	**Numbers (%)**				
Black	12 (80.0%)	24 (92.3%)	7 (77.8%)	7 (100%)	50 (87.7%)
White	3 (20.0%)	2 (7.7%)	2 (22.2%)	0	7 (12.3%)
Co-Morbidities	**Numbers (%)**				
Hypertension	3/13 (23.1%)	6/23 (26.1%)	3/7 (42.9%)	4/7 (57.1%)	16/50 (32.0%)
Diabetes	1/13 (7.7%)	1/26 (3.8%)	1/7 (14.3%)	1/7 (14.3%)	4/54 (7.4%)
Illicit drug use (former or current)	4/14 (28.6%)	5/26 (19.2%)	2/9 (22.2%)	1/7 (14.3%)	12/56 (21.4%)
Hepatitis	6/14 (42.9%)	8/26 (30.8%)	1/9 (11.1%)	2/7 (28.6%)	17/56 (30.4%)
Psychiatric disease	3/14 (21.4%)	7/26 (26.9%)	1/9 (11.1%)	2/7 (28.6%)	13/56 (23.2%)
HIV factors	**Median (IQR)**				
Years from HIV diagnosis	9.5 (6–13)	4.5 (1–10)	12 (5–15)	11 (5–17)	8.5 (3–12)
CD4 count (cells/mm^3)	284 (50–494)	256 (110–400)	403 (326–683.5)	667 (100–865)	315 (110–494)
Viral Load (copies/ml)	400 (20–32,233)	8,796 (1,045–21,791)	357 (20–400)	40 (20–115)	400 (43.5–15,723.5)
	Numbers (%)				
On cART	12 (85.7%)	13 (50%)	7 (77.8%)	6 (85.7%)	38 (67.9%)

care (Table 6) (54, 200).

To sum up, Patients who have *HIV* infection face an elevated danger of developing blood malignancies along with solid organ tumors. HAART has decreased *HIV* viral levels which both slows the progression to AIDS and minimizes opportunistic infections and hospital stays while protecting patients from death. The data from patients undergoing antiretroviral therapy reveals decreasing numbers of neoplastic lesions which demonstrates how HAART might fight cancer development. Laboratory evidence shows that antiretroviral drugs specifically protease inhibitors because multiple myeloma cells to halt their growth and die through apoptosis while nelfinavir creates a halt to cell division before causing melanoma cells to die through apoptosis. The *HIV* drugs Efavirenz (EFV) and Nevirapine (NVP) caused reversible cell proliferation reductions together with significant differentiation effects in primary human renal cell carcinoma cells. Some *HIV* medications that originated for inhibiting retroviral enzymes may serve as chemotherapeutic agents for cancer treatment. Current research lacks sufficient information regarding the difference in anti-proliferative properties between anti-*HIV* medications on *OC* cells (201, 202, 203, 204).

Prognosis and Survival Outcomes

The analysis of 52 research studies confirmed that cancer stem cell markers ALDH1, CD117, CD133 and CD44 demonstrate substantial value for *OC* prognosis and prediction. Research data demonstrates that OS and DFS become shorter when ALDH1, CD117 or CD44s markers increase in expression. The assessment of CSC markers together could provide a solid prognostic method for making better decisions regarding the treatment of OC patients (205, 206, 131, 207, 208). Otherwise, a functional homologous recombination (HR) assay has been devised to forecast both the primary chemotherapeutic response and long-term survival outcomes in *ovarian cancer* patients. This innovation stems from the established correlation between homologous recombination deficiency (HRD) and heightened platinum sensitivity, a critical determinant of responsiveness to poly (ADP-ribose) polymerase inhibitors (PARPi). Given the absence of reliable diagnostic methodologies

Table 7. Associations between HR score and therapeutic efficacy (209, 213, 214, 215)

	Patient ID	Tumor location	Tumor HR score	HR score-rea	Primary platinum response	Primary therapy outcome	Age at diagnosis	FIGO stage	Surgical strategy	Residual tumor after surgery (cm)	Progression after primary therapy	Time to progression (month)	Platinum free interval (days) in progressive disease	Survival/time to death (months)
HR deficient	EOC423	Omentum	3.3	3.3	Sensitive	CR	81	IIIC	NACT	0	No	-	-	Alive
	EOC782	Omentum	7.7	7.7	Sensitive	CR	60	IIIC	PDS	<1	Yes	32.2	831	Alive
	EOC44	Ovary	9.1	11.7	Sensitive	CR	61	IIIC	PDS	0	No	-	-	Alive
		Ascites	14.3											
	EOC737	Ascites	12.5	12.5	Sensitive	CR	69	IIIC	PDS	>1	No	-	-	Alive
	EOC148	Ovary	6.3	12.7	Sensitive	CR	70	IIIC	PDS	>1	Yes	12.3	231	Alive
		Adnex	19											
	EOC839	Mesentery	16.7	16.7	Sensitive	CR	77	IIIC	PDS	0	No	-	-	Alive
						CR 100% (6/6)	69.7(median) 60% 81(range)				No 67% (4/6)Yes 33%(2/6)	22.2(average)	531(average)	Alive 100% (6/6)

Table 7. Associations between HR score and therapeutic efficacy (209, 213, 214, 215)

HR low	EOC606	Ovary, left	22.2	22.2	Sensitive	CR	78	IIIC	PDS	0	No	-	-	Alive
	EOC415	Ovary, left Ovary, right Ascites Omentum Perito-neum	20 48.7 28.6 4.8 26.7	24	Sensitive	CR	65	IIIC	PDS	0	No	-	-	Alive
	EOC740	Ascites	24	24	Resistant	PR	60	IIIC	NACT	>1	Yes	9.1	63	Alive
	EOC864	Ascites	25	25	Sensitive	PR	69	IVB	NACT	<1	Yes	20	375	Dead to cancer /71.4
	EOC23	Ascites	25	25	Sensitive	CR	67	IIIC	PDS	0	No	-	-	Alive
	EOC732	Perito-neum	25	25	Sensitive	PR	68	IIIC	NACT	>1	No	-	-	Alive
	EOC498	Adnex Omentum	24 26.9	25.5	Sensiti-ve1	CR	54	IIIC	PDS	<1	No	-	-	Alive
	EOC1120	Ascites	27.3	27.3	Resistant	PR	68	IVB	PDS	<1	Yes	9.2	71	Alive
	EOC881	Ascites	28.6	28.6	Sensitive	CR	59	IIIC	NACT	<1	Yes	11.8	207	Dead to cancer /18.5
	EOC691	Ascites (p) Ovary(i)	40 23.8	31.9	Sensitive	PR	68	IVB	NACT	<1	No	-	-	Alive
						CR 50% (5/10)PR 50%(5/10)	65.6(medi-an) 54–69 (range)				No 60% (6/10)Yes 40%(4/1)	12.6(ave-rage)	179(avera-ge)	Alive80% (8/10) dead 20% (2/10) TTD = 45 (ave-rage)
HR proficient	**EOC221**	Ascites	38.5	**38.5**	Resistant	PD	78	IIIC	NACT	>1	Yes	2.8	83	Dead to can-cer/23.9
	EOC664	Ascites	44.4	**44.4**	Resistant	CR	61	IVB	NACT	<1	Yes	9.4	121	Dead to can-cer/35.8
	EOC26	Ascites (p) Ascites (r)	53.3 59.3	**56.3**	Resistant	PD	72	IIIC	NACT	0	Yes	4.2	0	Dead to can-cer/11.9
	EOC 933	Ovary, left	60	**60**	Sensitive	CR	74	IIIC	NACT	0	No	-	-	Alive
	EOC393	Ascites	78.3	**78.3**	Resistant	PD,b	74	IIIC	NACT	n.a.	Yes	2.1	8	Dead to cancer/2.1
						40% CR (1/5) 60% PD (3/5)	71.8(me-dian) 61–78(ran-ge)				No 20% (1/5)Yes 80% (4/5)	4.6(avera-ge)	53(average)	Alive 20% (1/5) dead 80% (4/5) TTD = 18.4(ave-rage)

Note: Enrolled in the PAOLA-1 trial subsequent to initial chemotherapy (ClinicalTrials.gov Identifier: NCT02477644). Abbreviations: I, interval; n.a. died during NACT, no interval debulking operation; P, primary; R, relapse; TTD, time to death. [a]For patients with multiple samples, HR score is calculated as average. [b]Died during chemotherapy.

to preemptively assess sensitivity to platinum-based regimens, researchers sought to develop an ex vivo functional HRD detection assay capable of predicting platinum responsiveness while simultaneously identifying patients suitable for targeted molecular therapies (Table 7) (209, 210, 211, 212).

Future Directions in Research

Research activity at the point where *Human Immunodeficiency Virus (HIV)* meets *ovarian cancer* requires special approaches and capabilities.

Merging Research Areas: Research now investigates how well checkpoint inhibitor immunotherapies function in treating *ovarian cancer* cases. Research into new strategies becomes essential because checkpoint inhibitors fail to achieve optimal results (216). Concurrently, studies on immunotherapeutic approaches in *HIV-positive* individuals have demonstrated encouraging outcomes, indicating prospective advantages that merit comprehensive exploration (217). The intersection of these disciplines holds the potential to yield groundbreaking therapeutic advancements for individuals afflicted by both conditions.

Gaps in Current Knowledge: A dearth of comprehensive data persists regarding the prevalence and clinical outcomes of *ovarian cancer* in *HIV-positive* women, impeding the formulation of personalized therapeutic strategies. Furthermore, the influence of *HIV*-induced immunosuppression on the progression of ovarian malignancies and their responsiveness to treatment remains inadequately investigated.

Potential for Integrated Therapies: The integration of antiretroviral therapy with novel oncological interventions, including PARP inhibitors and immunotherapeutic agents, presents a promising avenue. Synergistic combination regimens are currently under rigorous investigation to enhance clinical efficacy in the management of *ovarian cancer* (218, 219). The convergence of these therapeutic strategies has the potential to optimize treatment efficacy for individuals affected by both *HIV* and *ovarian cancer*. Conclude by underscoring the imperative for extensive research to elucidate the intricate interplay between *HIV* and *ovarian cancer* particularly with regard to enhancing early detection, refining treatment approaches, and improving clinical outcomes for this demographic (57, 220, 221, 222, 223, 224).

CONCLUSION

In conclusion, the available evidence regarding ovarian cancer among HIV-positive women highlights a complex and still insufficiently understood intersection between immunodeficiency and oncogenesis, warranting further investigation. Although some studies suggest a possible association between HIV infection and ovarian malignancy, the current evidence remains limited, heterogeneous, and largely observational. Chronic HIV infection, immune dysregulation, chronic inflammation, and antiretroviral therapy may represent biologically plausible contributing factors; however, their precise role in ovarian cancer risk has not been established. Given the multifaceted nature of this potential association, clinicians should maintain clinical vigilance for gynecologic symptoms and individualized risk assessment in HIV-positive women, particularly in those with a prolonged history of HIV infection. Moreover, future research should further investigate the molecular mechanisms that may link HIV-related immune dysfunction, chronic inflammation, and viral or host-related cofactors to ovarian cancer development. Addressing these factors will enhance our understanding of the possible pathophysiological relationship between HIV and ovarian cancer and may help inform future prevention and management strategies.

ACKNOWLEDGMENTS

The authors sincerely appreciate all researchers whose published work contributed.

Conflict of interest statement:

No relevant conflicts of interest associated with this article have been disclosed.

Author Contributions:

ABH: Development of the search strategy, abstract review, and final data extraction. PN: Development of the search strategy, abstract review, and final data extraction. Both authors had full access to the study data. All authors have read and approved the final manuscript and accept responsibility for the integrity and publication of the work.

Data Availability: All data compiled is in the manuscript.

Funding Statement:

No funding was received to assist with the preparation of this manuscript.

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