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Pathology of HIV/AIDS: Lessons from Autopsy Series

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1. Introduction

HIV infection is a global disease and despite considerable efforts of the international community it is a main cause of human mortality (UNAIDS, 2009). Morphological insights into HIV/AIDS are based on the study of clinical cases by means of biopsy and autopsy. Morphological changes during development of HIV infection and, especially, through AIDS progression are variable and specified mainly by characteristics of widespread secondary infections and tumors. Opportunistic infections account for approximately 80% of deaths in patients with AIDS and their spectrum is constantly changing, as a result of improvements in treatment options and prophylaxis along with the increasing life span of HIV-infected individuals. Postmortem examinations provide important diagnostic and epidemiological data and represent a most reliable source for estimation of the full spectrum of diseases in individual patients and the general population.

2. Pathomorphology of HIV/AIDS

Morphology of HIV/AIDS is manifested by wide range of indicative (secondary) diseases while specific changes caused by HIV are mainly detected in immune system at the early stages of infection and in central nervous system.

Lymphadenopathy is the marked feature of acute HIV infection defined as generalized enlargement of lymph nodes. Histologically, this process passes through a series of changes: hyperplasia, involution, depletion, and sclerosis (Baroni & Uccini, 1993). In the stage of hyperplasia, the lymph nodes are characterized by disorderly grouped multiple follicles with 'starry sky' pattern due to arrangement of macrophages. Formation of multinuclear cells resembling symplasts is result of merging of lymphocytes infected by virus. With the progression of disease, lymphoid depletion becomes extensive and a fibrovascular carcass appears more evident along with increasing vascularity (angiomatosis). Finally, lymph nodes harbor 'burnt-out' appearance. Although profound depletion of lymphoid tissues is driven by cytotoxic effect of HIV but there is no histologic picture diagnostic of this condition (O'Murchadha et al., 1987).

Large proportion of patients at different stages of disease has morphological proofs of HIV-induced brain damage (Kibayashi et al., 1996). HIV neuropathology is comprised of

following patterns (in order of appearance): lymphocyte infiltration of the leptomeninges, microglial nodules formation and HIV encephalitis. The latter lesion consists of numerous foci with mononuclear cells typical of small macrophages, microglia, and multinucleated giant cells. The giant cells are the hallmark of HIV infection since viral antigens can be detected in their cytoplasm (Gyorkey et al., 1987).

Development of indicative diseases which include opportunistic infections and secondary neoplasms which reflects severe deficiency of immune system and in most of cases determines progression of the disease to full-blown AIDS. Morphological descriptions given below represent our common findings of infectious and neoplastic diseases in AIDS.

2.1 Morphology of mycobacterial infections in HIV patients

Tuberculosis in HIV-patients is characterized by a prevalence of its generalized form with extensive dissemination and acute progression of specific processes. Notable histological features are loss of granuloma formation and abundance of necrotic changes. Generally, all the forms of tuberculosis seen in the terminal stages are actively progressive. The main forms of tuberculosis are generalized, pulmonary (often disseminated) and extrapulmonary. Thus, various organs are affected, most often the lungs, lymph nodes, liver, kidneys, spleen, intestine, and central nervous system (Smith et al., 2000). Tissue reaction in the terminal stage shows typical tuberculous granulomas with giant and epithelioid cells in only 20% of lesions, whereas the remaining 80% demonstrates numerous foci of nonreactive caseous necrosis abundant of acid-fast bacilli (Parkhomenko et al., 2003).

Pulmonary tuberculosis is manifested as a bilateral disseminated type or polycavernous variant. In disseminated tuberculosis, foci of specific lesions (granulomas) comprise large central zones of caseous necrosis surrounded by a few inflammatory cells. Giant cells are uncommon. Ziehl-Neelsen staining shows numerous acid-fast bacteria in the foci of caseous necrosis. All these histological signs characterize tuberculosis as progressive and highly active. Macroscopic study of the lungs often reveals miliary disseminated tuberculosis, while macrofocal dissemination and caseous pneumonia are rare. The pattern of dissemination is bilateral, with a predominance of micronodular, miliary and submiliary types. Tubercles evenly spread to the whole organ or localized to one of the lobes. In a large proportion of cases, macroscopic detection of tuberculous changes in lungs is difficult, but histological examination reveals miliary and submiliary necrotic foci (Berdnikov et al., 2011). The characteristic microscopic picture is a predominance of alterative and exudative changes with the lack of a productive component of inflammation or its minimal manifestation (Fig. 1a). The latter is marked by the absence of signs of encapsulation and organization of inflammatory foci. Classic granulomas are infrequent and only few of them contain giant cells of Langhans (Fig. 1b). Initially, there is formation of colonies of *Mycobacteria* in the pulmonary parenchyma, which is accompanied by cellular infiltration with a significant predominance of polymorphonuclear leucocytes. The cells phagocytose the bacteria and this step is marked by karyorrhexis. Later, this process is associated with massive breakdown of leucocytes resulting in necrosis and microabscesses. Tissue sections stained by Ziehl-Neelsen showed numerous acid-fast bacteria in the foci of caseous necrosis. An exudative reaction in the form of serous-fibrinous pneumonia or fibrinous-purulent pneumonia with predominance of neutrophilic leucocytes is detected at the periphery of caseous foci. Such

exudation may extent from lobular up to sub-lobar area. Some alveoli contain accumulations of foamy macrophages that are characteristic for typical tuberculous inflammation. There is an increase in the thickness of the pleura caused by extensive hyperemia and edema. The intrathoracic lymph nodes are also affected, enlarged (3–4 cm in diameter), and aggregated. Partial or total caseous lymphadenitis is detected with the spread of inflammatory processes to the surrounding soft tissues. Evident reduction of follicular structures and lymphoid depletion is a characteristic feature of these lymph nodes.

Extrapulmonary tuberculosis is detected as a component of a generalized type of tuberculosis. Monomorphic miliary foci of caseous necrosis are found in various internal organs, more often in the spleen, kidneys, liver, and rarely in the meninges, peritoneum, exo- and endocrine glands (pancreas, adrenals, prostate, thyroid, ovaries). As a whole, in cases of generalized tuberculosis, *Mycobacteria* cause alterative and exudative reactions simultaneously in several organs with the mean number of organs involved is 5.4 (own data). Most of the foci are suspected to be spread via hematogenous dissemination from lungs. Histopathology of the parenchymatous organs reveals monomorphic miliary nodules of caseous necrosis with rare giant cells, as in the lungs. In many cases, tubercles are not visible by visual inspection. In the spleen, the foci of caseous necrosis have a tendency to fuse and may cover up to 50% of the cut surface.

Tuberculous meningitis is characterized grossly by typical basilar localization with poorly detected gray-white exudates and tubercles in the subarachnoid space. Microscopic examination of the meninges reveals evident hyperemia and edema accompanied by alterative reactions. The latter is manifested as areas of caseous necrosis extensively infiltrated by polymorphs, lymphocytes, and macrophages. Various types of vasculitis such as endovasculitis, panvasculitis, thrombovasculitis, and perivasculitis are evident. Perivasculitis is more often present with edema and excessive mononuclear, neutrophilic, eosinophilic, and plasma cell infiltration in all layers of the vessel wall (Fig. 1c). Destructive process may extent into brain tissue with formation of localized abscesses.

Mycobacterium avium-intracellulare (MAI) infection leads to massive necrotic destruction of lymph nodes with minor involvement of the lungs. Mostly granulomas are difficult to detect throughout the inner organs by naked eye. The only exception is spleen which is filled with miliary granulomas in roughly half of cases. Different groups of visceral lymph nodes are enlarged and show characteristic yellow tone of cut surface. Microscopically, proliferation of large round to elliptical striated pale blue macrophages is noted. Cytoplasm of these cells is packed with huge number of acid-fast bacilli. Well-formed granulomas with fibrosis, necrosis, and epithelioid histiocytes are present in less than one third of cases (Klatt et al., 1987).

2.2 Morphology of bacterial infections

Bacterial Pneumonia

There is a broad spectrum of causative agents of pneumonia revealed by microbiology. Besides typical microflora, bacterial pneumonia can be caused by opportunistic agents, which are activated under immunodeficiency. The most common causative agents of pneumonia are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Escherichia coli* (Afessa et al., 1998).

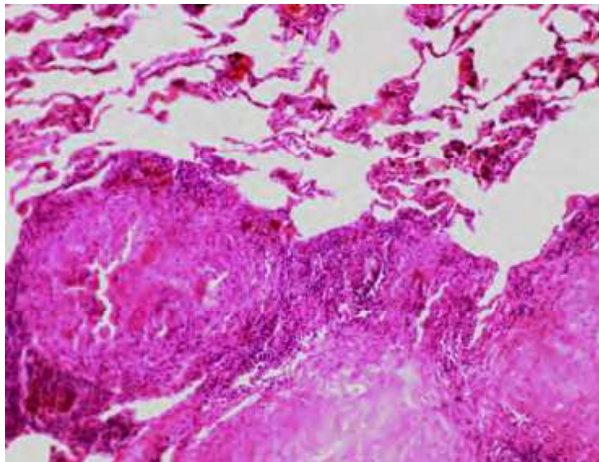
Hematoxylin and eosin together with Gram staining of sections of lungs helps in revealing nonspecific microflora. At autopsy, staining of smears of lung sections using Romanovskii-Giemsa and Gram stains is also useful in establishing the nonspecific character of microflora in cases of bacterial pneumonia. Bacteriological culture of lung tissue helps in revealing the nature of the causative agents of pneumonia most accurately. Grossly, patchy areas of red or grey consolidation involve more often the lower zones of the lungs. On cut surface, these patchy consolidated lesions are dry, granular, firm, red or grey in color, slightly elevated over the surface and are often located around a bronchiole. Histologically, suppurative exudate, consisting of neutrophils with admixture of fibrin, fills alveoli and alveolar septa are dilated by congested capillaries and leucocytic infiltration. Often, the course of pneumonia in HIV-infected patients has a tendency to form microabscesses, and in such cases, the microscopic changes resembles to microfocal dissemination in pulmonary tuberculosis. In microabscesses, purulent necrotic foci are found with expressed perifocal exudative reaction, which strengthened their resemblance to pulmonary tuberculosis in HIV-infected patients.

Sepsis

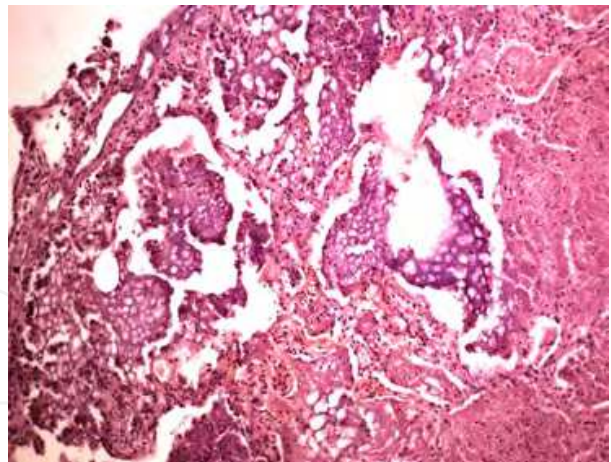
Pneumonia and primary bloodstream infections are the main sites of infections for almost all patients with sepsis, followed by angiogenic-related bacteremia originated from thrombophlebitis in intravenous drug users or from venous catheter in bedridden patients and urinary tract infections. Nosocomial infections compose the major part of etiology of severe sepsis. Microbiology of infections is comprised of different species, mostly *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Staphylococcus spp.*, while *Streptococcus spp.*, *Escherichia coli* and *Salmonella spp.* are detected with lower frequency (Japiassú et al., 2010). Microorganisms impact small vessels in the primary site and cause local injury both by obstructing the vessels and by releasing toxins. Subsequently a combination of necrosis, hemorrhage and suppuration occurs, with further formation of pyemic abscesses in the various organs and their distribution depends on the site of the original septic thrombosis. Microscopically, pyemic abscesses are typically surrounded by a zone of hemorrhage and an early lesion may show a central zone of necrosis often containing huge numbers of bacteria. This is surrounded by a zone of suppuration and an outermost zone of acutely inflamed and often hemorrhagic tissue. In septic thrombosis of major veins, larger fragments may be released into the circulation, and by impacting in arteries give rise to correspondingly larger foci of necrosis and suppuration (septic infarcts). In case if it involves heart, pyogenic bacteria may produce endocarditis and severely damage cardiac valves. The vegetations on valve are tend to break down and the valve cusps are largely covered by crumbling masses, which consist of layers of fibrin containing clumps of bacteria enclosed by a zone of leukocytes, macrophages and granulation tissue. The substance of the cusps may be extensively destroyed by suppuration.

2.3 Invasive fungal infections

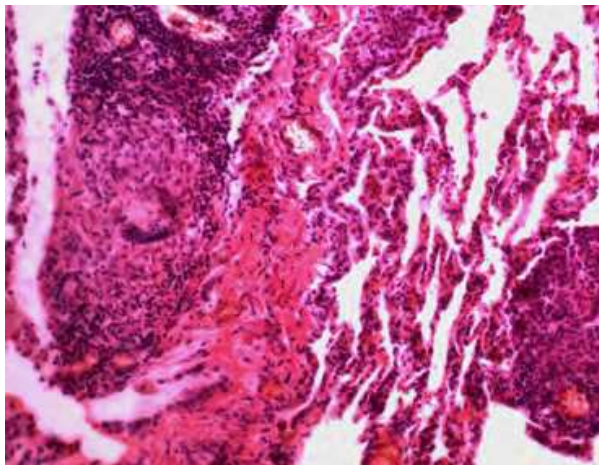
Pneumocystis jirovecii (former *Pneumocystis carinii*) typically produces pneumonia that is widespread throughout the lungs with a chronic course of disease and rapid progression. Pulmonary pneumocystosis is a disease caused by intense multiplication of relatively pathogenic single-celled saprophyte *Pneumocystis jirovecii* in the human respiratory tract.



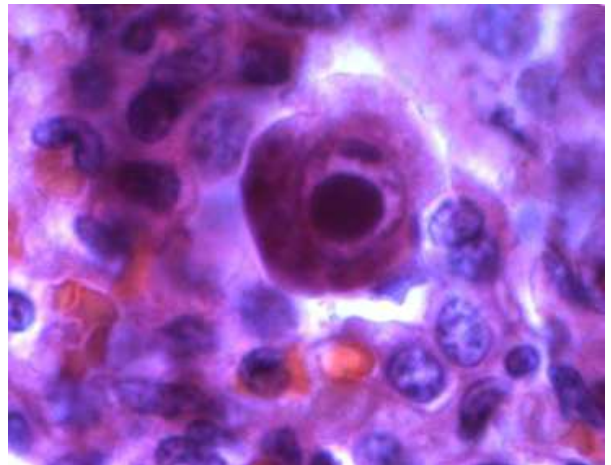
(a) Pulmonary tuberculosis, foci of caseous necrosis. H&E, $\times 100$



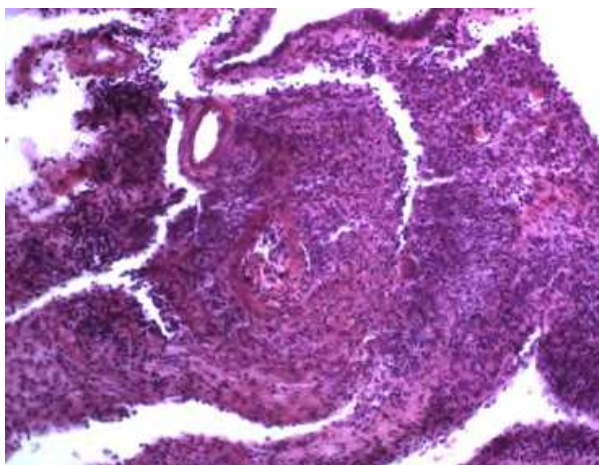
(d) Pneumocystic pneumonia, foamy exudate. H&E, $\times 100$



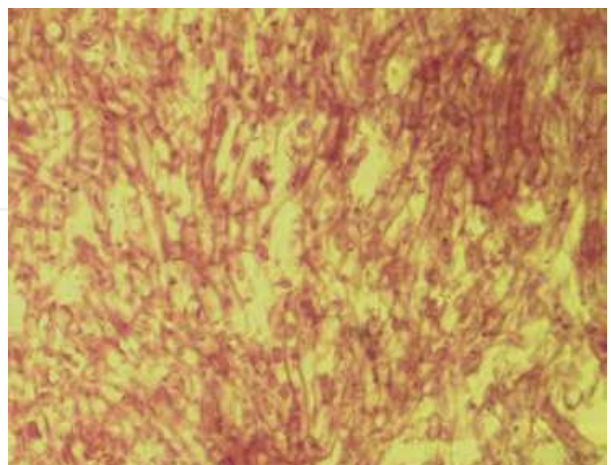
(b) Pulmonary tuberculosis, granuloma with giant cell. H&E, $\times 140$



(e) Cytomegalovirus infection of lung, cell with 'owl-eye' appearance. H&E, $\times 1200$



(c) Tuberculous meningitis, panvasculitis with alteration. H&E, $\times 140$



(f) Pulmonary aspergillosis, branching hyphae of fungus. PAS, $\times 600$

Fig. 1. Microscopic patterns of opportunistic infections in AIDS

The terminal period of pneumocystosis is pneumonia, manifested in the later stages of HIV infection, which often leads to death. The gross appearance resembles to pneumonic consolidation. The cut surface of the lung is pale pink with scattered areas of congestion and rarely hemorrhages. Microscopically, in the edematous stage, characteristic homogenous, foamy protein-containing eosinophilic exudate is found in the alveolar lumen (Fig. 1d). This is a pathognomonic sign of pneumocystic pneumonia. Neutrophils, macrophages and plasma cells are detected around the collections of *Pneumocystis jirovecii*.

Cryptococcus neoformans in immunocompromised hosts may spread from lungs, which is the site of primary infection, to distant organs and most frequently affecting the central nervous system and causes meningitis. Pulmonary manifestations exhibit pneumonitis, pulmonary nodules or less commonly pleural effusions. Sometimes variably sized pale soft granulomas are grossly visible in the lungs. If fungi with capsules are numerous, a grossly apparent mucoid exudate may be seen in the cerebral ventricles or on the meninges. Microscopically, the yeast cells appear pale blue and ovoid while the capsule is round and clear. Inflammatory reaction is weak and represented by a few scattered lymphocytes or macrophages with phagocytized organisms. PAS stain is effective for detection of the capsule and nucleus of the organisms.

Candida albicans infection is one of the most prevalent in patients with AIDS, ranging from localized skin and mucosa lesions to widely disseminated disease. Characteristic gross findings of candidiasis are prominent in the pharynx, larynx, and trachea with invasion into principle bronchi, which includes a pseudomembranous form with white, elevated mucosal plaques. Bronchopulmonary aspergillosis and candidiasis are characterized by the collection of fungal mycelia in the lumen of small bronchi and invasion of fungus into the acini. *Candida* microabscesses are common and they had a typical polymorphonuclear leucocytes infiltration. Histologically, *Candida* organisms could be identified by their size, budding property, and pseudohyphae. The pseudohyphae could be distinguished from *Aspergillus* hyphae by the lack of branching, the smaller size, and frequent absence of true septations in the former. Histological diagnosis may be confirmed using the Romanovskii staining technique, which is helpful in differentiation between *Candida* and *Aspergillus*. Bronchopulmonary aspergillosis is characterized by the collection of branching mycelia of *Aspergillus* in the bronchial lumen with involvement of the bronchial wall and further invasion of the fungus into the acini (Fig. 1f).

2.4 Viral and parasitic infections

Cytomegalovirus (CMV) infection is one the most prevalent secondary diseases in AIDS. It is featured by multiple organs involvement, including lungs, digestive system, brain and eyes. CMV infection proceeds diversely from latent infection to severe acute generalization in the later stages of HIV infection. Microscopically, CMV lesions appear as characteristic metamorphosis of alveolar and bronchial epithelium (Fig. 1e). The persistence of viruses in the epithelial cells leads to cytomegalic giant cell formation. Alveolar cells increase in size up to 25–40 μm . About 1–2 nuclear inclusions are detected containing viral particles in the chromatin in each cell and there is a thin perinuclear clear halo. The nucleus of each affected cell is usually eccentrically positioned and the cell border is not prominent. Additionally, the cytoplasm of affected cells may contain coarse dark basophilic bodies. Characteristic infiltrative changes and CMV transformations are numerous. Moderate cytomegalic transformation of alveolar and bronchial epithelial cells (2–3 typical cells in the form of an

'owl-eye' in the field of view) is accompanied with focal accumulations of serous fluid and protein masses in the alveolar cavities along with admixtures of macrophages and weak infiltration of interstitial tissue. If the lung changes consist of diffuse persisting alveolitis with CMV transformation (up to 20 cells per field of view), then this process is accompanied by extensive fibrosis, but uncommonly leads to the formation of a 'honeycomb-like' appearance of the lungs. The outcome of CMV infection of the lungs is peribronchial and widespread interstitial fibrosis with thickening and vast deformation of the interalveolar septa. Thus, heterogeneous patterns of CMV infection of the lung represent continuous progression of disease and include the following events as virus-induced transformation of the cells, pneumonias with cavity formation, productive granulomatous alveolitis and eventually pulmonary fibrosis (Parkhomenko et al., 2004).

Toxoplasma gondii is a protozoan parasite which is highly prevalent among humans and animals throughout the world. Immunocompromised patients are especially prone to develop disseminated toxoplasmosis, either from acute exposure to the organisms or from reactivation of latent infection. Multiple organ systems are often involved, including the CNS, heart, lungs and skeletal muscle. Damage to the CNS by *Toxoplasma gondii* is characterized by numerous foci of enlarging necrosis and microglia nodules. The former are often resolved with cyst formation or calcification. Presence of many brain abscesses with almost universal involvement of the cerebral hemispheres is the most characteristic feature of toxoplasmic encephalitis in AIDS patients. The diagnosis of toxoplasmosis is readily made from histologic analysis of tissue specimens by observing any of the three infectious stages of *T. gondii*: tachyzoites in groups, bradyzoites (parasitic tissue cysts) or sporozoites within oocysts. Tachyzoites and cysts are seen in and adjacent to necrotic foci near or in glial nodules, perivascular regions, and even in uninvolved cerebral tissue. Reactive inflammatory reaction is comprised of mixed infiltrate distributed in patchy pattern.

2.5 HIV-associated neoplasia

Kaposi's sarcoma is a low-grade mesenchymal tumor which arises initially as an angioproliferative disorder caused by *Kaposi's sarcoma-associated herpes virus* (Du et al., 2007). Skin involvement is common and manifested by the presence of red to red-purple lesions ranging from flat patches to slightly raised plaques and nodules. Visceral involvement frequently includes the lung, lymph nodes, and gastrointestinal tract. Microscopically, *Kaposi's sarcoma* features clusters of tiny apparent capillaries budding off normal blood vessels. It grows as massed bundles of spindle cells, with red blood cells in slits between them. Hemosiderin pigmentation and hyaline globules usually accompany the spindle cell proliferation. Tumor has an ability to infiltrate around large vascular structures, near epithelial or mesothelial surfaces, or near the capsules of organs.

Non-Hodgkin lymphomas (NHL) risk in AIDS patients is increased more than 70 times comparing with general population (Frisch et al., 2001). Malignant non-Hodgkin's lymphomas (mostly intermediate- to high-grade tumors) exhibit two major patterns which include systemic and CNS lymphomas. These lymphomas often show evidence of *Epstein-Barr virus* as etiologic agent (Fassone et al., 2002). AIDS-related lymphomas consistently determine a B-cell phenotype and are histogenetically related to germinal center or postgerminal center B-cells in the vast majority of cases. About 80% of NHL's in AIDS arise systemically, either nodally or extranodally, while 20% arise in the central nervous system. Almost any extranodal site can be involved with predominance of bone

marrow, gastrointestinal tract and liver. NHLs appear as small infiltrates, focal nodular lesions, or larger tumor masses with accompanying necrosis and hemorrhage. Microscopically, tumors generally referred to diffuse large B-cell lymphomas or high-grade B-cell (small non-cleaved) Burkitt-like lymphomas, according to REAL classification. Immunohistochemistry is a routine diagnostic tool in typing of these lesions.

3. Autopsy series

AIDS was recognized in 1981 for the first time, resulting in the deaths of more than 25 million people. Since the late 1990s approximately 2 million HIV-infected persons are reported to have died annually (UNAIDS, 2009). Distribution of the regions with the highest death tolls is determined by the prevalence of HIV infection. Countries of Sub-Saharan Africa are the worst-affected, followed by South and South-East Asia. Most countries with high rates of AIDS prevalence have published reports on autopsy series to date (Fig. 2). Currently, there is a global decline of autopsy rates as a consequence of improved patient management, introduction of etiologic therapy and preventive measures. However such advances are available only in developed countries, where postmortem examination has lost the status of routine diagnostic procedure. Concurrently only few recent reports from Sub-Saharan Africa are available while the pace of HIV epidemics is still very high. Moreover, some countries with high AIDS burden (more than 500,000 infected) including Thailand, China and Ukraine are yet to present large autopsy series.

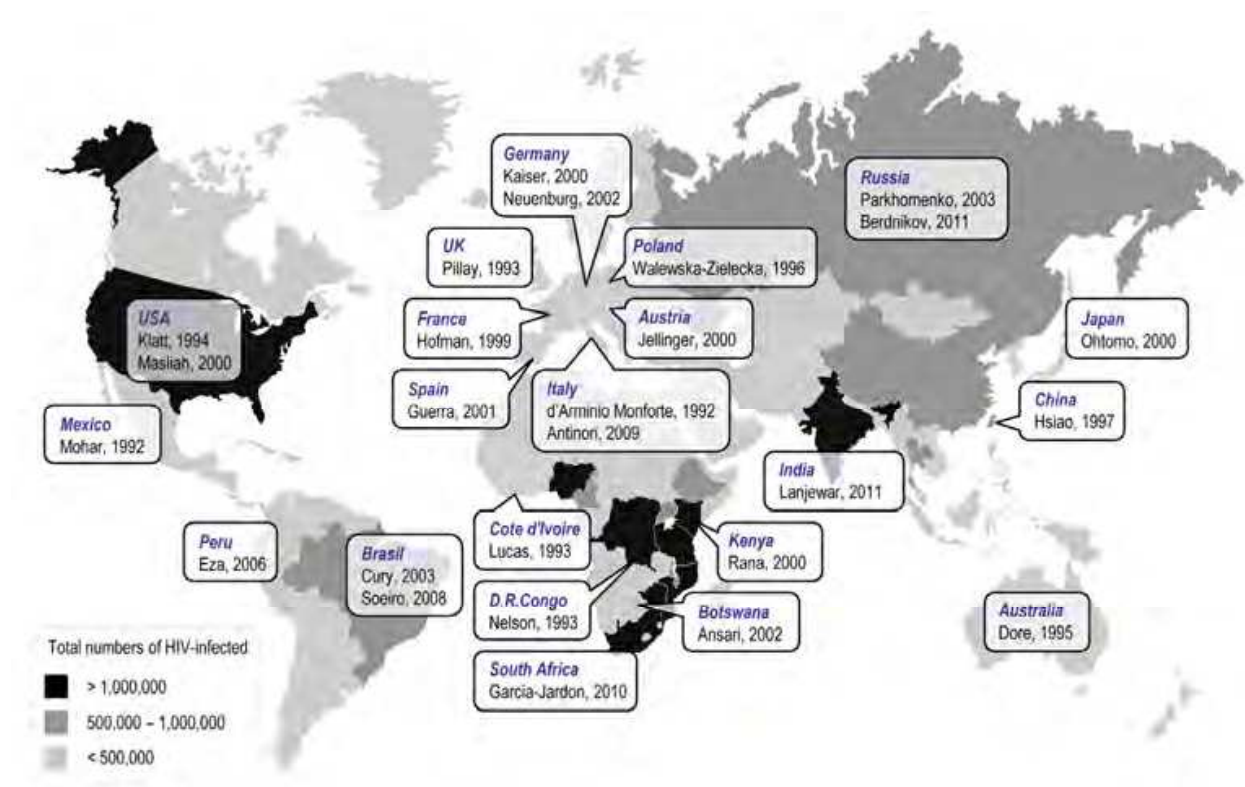


Fig. 2. Worldwide representative autopsy series

3.1 Value of autopsy

Since the first years of HIV/AIDS pathology has contributed significantly to study of new disease. Before mid-1990s various changes of organs and systems studied with different pathological techniques were described in numerous publications. The data taken from the study of autopsy series have shown that postmortem examination is extremely valuable for determining wide range of AIDS-related diseases. Diagnostic role of the autopsy is enhanced considerably by employment of histological examination of the organs. Such specimens can be further proceeded to staining with special techniques useful in detection of microorganisms or immunohistochemistry and even to molecular biological techniques. Thus, complete postmortem study allows determining the cause of death and contributed pathologies, it may identify diseases and etiological agents that were clinically unsuspected or undiagnosed. By providing these types of data, the autopsy serves as an important measure in monitoring the quality of care, basically comparing antemortem with postmortem findings. Autopsy remains established tool for obtaining epidemiological information about diseases and producing vital statistics, since systematic postmortem examination provides representative data on the main pathologies in distinct communities and permits evaluation of changes that may occur over time (Lanjewar, 2011; Lyon et al., 1996). Postmortem surveillance is vital for monitoring the course of HIV-infection and promotes clinicians awareness (Sehonanda et al., 1996).

However, over the past decades, autopsy rates have markedly declined all over the world due to various reasons (Table 1). Advances in laboratory and radiological diagnostics contribute in recognizing different AIDS-related diseases and diminish diagnostic value of autopsy.

Benefits	Limitations
<p><i>Diagnostic value:</i></p> <ul style="list-style-type: none"> - gross findings, - histological analysis, - correlations with antemortem diagnosis <p><i>Epidemiological needs:</i></p> <ul style="list-style-type: none"> - death records, - trends over time periods <p><i>Educational goals:</i></p> <ul style="list-style-type: none"> - for students, - for professionals (clinical conferences) <p><i>Scientific potential:</i></p> <ul style="list-style-type: none"> - case reports, - series reports, - sample collection/further reevaluation 	<p><i>Difficulties in obtaining consent</i></p> <p><i>High efficiency of clinical diagnostic tools:</i></p> <ul style="list-style-type: none"> - laboratory diagnostics, - diagnostic radiology, - endoscopy <p><i>Risk of infection for staff</i></p> <p><i>Choice of 'alternative autopsy' techniques:</i></p> <ul style="list-style-type: none"> - needle autopsy, - virtual autopsy, - verbal autopsy <p><i>High costs</i></p>

Table 1. The AIDS autopsies today: *Pros & Cons*

Health care systems of developed countries offer high-quality diagnostic opportunities for HIV patients, while in developing countries such options have limited availability. Another one concern is that most relatives of died patients are not willing to provide consent for an autopsy because of cultural, traditional and other beliefs (Garcia-Jardon et al., 2010). It is important for clinicians to approach families for autopsy consent. From the other hand, some pathologists and technicians avoid to carry out autopsies on HIV infected cases, because of risk to be infected (Lanjewar, 2011). A major challenge in applying autopsy for AIDS cases is the rising trend of so-called 'alternative autopsy' techniques. Whereas incomplete autopsies such as examination of selected organs or needle autopsy may be accepted partially as being equivalent to a full autopsy, non-invasive procedures like virtual autopsy and echopsy cannot substitute for conventional necropsy techniques (Burton & Underwood, 2007). Verbal autopsy which appears to be gaining acceptance in developing countries (Bhattacharya & Neogi, 2008) is in no way an objective diagnostic technique. Postmortem examination should include collection of organs specimens for histological study; any exception to this rule will markedly decrease the value of autopsy.

3.2 Results

We have analyzed the largest autopsy series from different continents that covered the time period from 1982 to 2011 (Table 2). The main focus was on the prevalence of AIDS-indicative diseases and their distribution according to time periods and geography. Opportunistic infections were the most common autopsy findings, followed by less frequent secondary neoplasms.

Mycobacterial infections were detected in all the series with the lowest frequency around 20% (Afessa et al., 1998; Guerra et al., 2001; Soeiro et al., 2008). In developed countries such as Italy, Germany and Japan, the prevalence of tuberculosis in autopsies of patients with HIV/AIDS is 5-7%, whereas these rates were found to be 38-59% mostly in developing countries (Ansari et al., 2002; d'Arminio Monforte et al., 1992; Hsiao et al., 1997; Kaiser et al., 2000; Lucas et al., 1993; Ohtomo et al., 2000). Pulmonary lesions tend to hematogenous spread, thus the disseminated variant was described in 60-90% cases (Ansari et al., 2002; Cury et al., 2003; Parkhomenko et al., 2003; Rana et al., 2000; Soeiro et al., 2008). Extremely high rates of tuberculosis were reported in recent studies from Russia and India, 82% and 68%, respectively (Berdnikov et al., 2011; Lanjewar, 2011). Emergence of tuberculosis became obvious only in the last decade, when dramatic increase of this infection was implicated as a prime cause of death in AIDS patients. The main reason for such burden in Russia is the overlapping of prior independent epidemics of HIV and tuberculosis with subsequent merging and fast spread through neglected population groups like intravenous drug users, prisoners, alcoholics, homeless persons. Modern HIV-associated tuberculosis is a highly aggressive destructive process in the lungs caused by multidrug resistant strains of *Mycobacteria* and characterized by widespread dissemination and extrapulmonary involvement (Berdnikov et al., 2011).

Currently MAI infections are not of major significance, but they featured notably in the early series from USA and Europe (Guerra et al., 2001; Jellinger et al., 2000; Klatt et al., 1994; Masliah et al., 2000).

Country	USA	USA	USA	USA	USA	Austria	Spain	Botswana	Brasil	Russia	Brasil	South-Africa	Russia	India	Russia
Source	Kiattl, 1994	Lyonn, 1993	Sehonanda, 1996	Alfessa, 1998	Maslah, 2000	Jellinger, 2000	Guerra, 2001	Ansari, 2002	Scoiro, 2008	Parfenovko, 2003	Scoiro, 2008	Garcia-Jardon, 2000-2006	Berdnikov, 2011	Lanjewar, 2011	own data (unpublished)
Period	1992-1993	1984-1993	1987-1993	1985-1996	1992-1996	1993-1996	1997-1997	1997-1999	1991-2003	1991-2003	1991-2003	2000-2006	2003-2010	1998-2007	2009-2011
Cases	565	279	168	233	390	260	150	104	92	321	250	86	264	223	155
Opportunistic Infections															
Mycobact															
TB	76	64	45	13	15	12	42	36	25	99	36	25	216	152	72
MAI	104	104	26	31	36	17	2	15	15	48	15	17	7	48	1
Bacterial															
Pneum	52	81	26	98	149	14	24	4	91	23	36	4	26	40	26
Sepsis	32				85	1	4	2	36	5	4	8	10	6	6
Meningitis					138	1	2		4	5				1	1
Viral															
CMV	286	128	36	40	196	127	19	16	33	59	33		3	35	10
HSV	92	20			11	11	1			19				16	1
Fungal															
PCP	308	80	55	56	100	30	21	11	68	6	7	7	6	11	17
Asperg	6	3	9	2	12	12	3		1	1	9	6	1	1	1
Cryptoc	78	25	9	23	25	25	3	7	9	3	6	7	9	18	5
Cand	240	30	23	6	119	46	1		6	3	3	1	44	6	9
Histoplasma	13	29	3	2	2	2			5	3	3	1	3	3	
Parasitic															
Toxo	51	9	5		11	18	1	1	18	22	18	1		15	6
Cryptosp	5	7							5		5	1		6	3
Helminthes														3	1
Secondary Neoplasms															
KS		138		19	41	41	1	11	11	33	11	1	2	2	2
NHL		81		3	20	17	13	3	2	3	5	1	6	8	2
Frequency hierarchy	CMV	PCP-CMV	PCP	Pneum	CMV-Bact	Bact-CMV	PCP-CMV	TB	Pneum-CMV	TB	Pneum-PCP	TB	TB	TB	TB
	PCP-Bact	PCP-CMV	PCP	PCP-CMV	PCP	PCP	PCP	PCP	PCP	PCP	PCP	PCP	PCP	PCP	PCP

Abbreviations: MycoBact, mycobacterial infections; TB, tuberculosis; MAI, *Mycobacterium avium-intracellulare* infection; Pneum, pneumonia; CMV, *Cytomegalovirus* infection; HSV, *Herpes Simplex Virus* infection; PCP, pneumocystic pneumonia; Asperg, aspergillosis; Cryptoc, cryptococcosis; Cand, candidiasis; Histoplasma, histoplasmosis; Toxo, toxoplasmosis; Cryptosp, cryptosporidiosis; KS, Kaposi's sarcoma; NHL, non-Hodgkin's lymphoma; Bact, bacterial infections

Table 2. Autopsy findings from the largest autopsy series.

Similarly, bacterial infections in the same way as tuberculosis showed a marked rise in the last decades and represent an important cause of mortality in AIDS patients. Bacterial pneumonias were identified in 21-36% of cases from low- and middle-income countries (Ansari et al., 2002; Garcia-Jardon et al., 2010; Lanjewar, 2011; Soeiro et al., 2008). Early American sets often not mentioned pneumonias apart from pyogenic infections like sepsis, because they were included in the list of AIDS criteria subsequently. HIV patients are prone to nosocomial pneumonias caused by bacterial associations which demonstrate relapsing course with complications such as abscess formation and pleural effusion (Parkhomenko et al., 2003).

The prevalence of *Cytomegalovirus* infection ranges from 13-19% in African, Indian and Brazilian series to 46-69% cases from USA and Europe (Jellinger et al., 2000; Klatt et al., 1994; Lyon et al., 1996; Masliah et al., 2000; Pillay et al. 1993; Walewska-Zielecka et al., 1996). The highest rates of 74-76% were described in Japan and Australia (Dore et al., 1995; Ohtomo et al., 2000). Among invasive fungal infections pneumocystosis exhibits most significant decline due to effective prophylaxis and introduction of highly active anti-retroviral therapy (HAART). Early reports described high prevalence of pneumocystic pneumonias in more than half of all patients (Klatt et al., 1994), however recent studies could reveal *Pneumocystis jirovecii* pneumonia in less than 10% cases (Parkhomenko et al., 2003). Low levels of pneumocystosis are also specific for African countries regardless time period (Garcia-Jardon et al., 2010; Lucas et al., 1993; Nelson et al., 1993). A large retrospective study of an Italian cohort showed that the prevalence of opportunistic mycoses decreased over time, owing mainly to a significant decrease in pneumocystosis and cryptococcosis, whereas the prevalence of aspergillosis and histoplasmosis remained relatively stable while that of candidiasis tended to increase in the last years (Antinori et al., 2009). Rates of toxoplasmosis showed no significant variation for decades and comprise 1-10% of cases (Cury et al., 2003; Guerra et al., 2001; Sehonanda et al., 1996). The levels of HIV-related neoplasms seem to be decreasing over time, which was demonstrated for both non-Hodgkin's lymphomas and Kaposi's sarcomas in reviewed series (Jones et al., 1999; Launay & Guillevin, 2003).

The main patterns of organ/system involvement in AIDS are pulmonary, generalized or system isolated (CNS, digestive system). In most autopsy series of HIV-infected patients, pulmonary pattern was the most common with an incidence of 60-88%, followed by the CNS (60-80%), and the gastrointestinal tract (Concepcion et al., 1996; Cox et al., 2010; Hofman et al., 1999; Jellinger et al., 2000; Mohar et al., 1992; Sehonanda et al., 1996). Opportunistic mono-infection was observed on the highest level only in 40% cases, while most postmortem studies detected several microbial agents (Rana et al., 2000; Soeiro et al., 2008).

Cases with advanced CNS alterations have a high frequency of opportunistic infections and neoplasms (Masliah et al., 2000). A generalized pattern may be caused by virtually all opportunistic agents, but the most disseminating microorganism today is *Mycobacterium tuberculosis* (Parkhomenko et al., 2003).

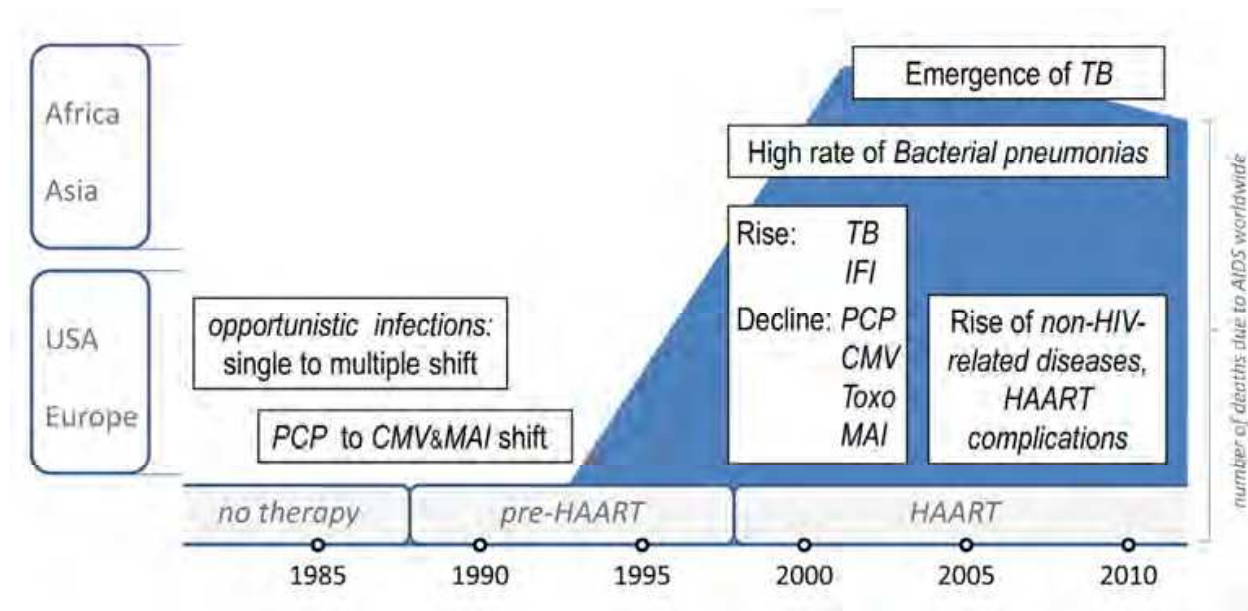
Not all deaths of AIDS patients are related to HIV. The percentage of deaths from AIDS-related diseases has decreased, especially in those countries where highly active antiretroviral therapy is widely available. Non-AIDS causes in high-income countries account for at least a third of deaths, and include non-natural causes such as drug overdose, suicide, and violence along with various somatic diseases (Kohli et al., 2005; Krentz et al., 2005). Important non-HIV-related complications contributing to mortality of AIDS patients

are chronic liver diseases, cardiovascular pathology and malignancies (d'Arminio Monforte, 2009; Friis-Møller et al., 2010; Lucas et al., 2008; Sackoff et al., 2006). Cases of hepatic involvement are extremely common in HIV-infected cohort of intravenous drug users with HCV co-infection which may die from liver cirrhosis or necrotizing liver failure (Guerra et al., 2001).

One of the important utilities of autopsy is the correlation between antemortem and postmortem diagnosis. A recent review from the UK spanning 23 years showed that the autopsy findings altered the primary diagnosis in 70% of cases, and that 36% of opportunistic infections were not diagnosed prior to death (Beadsworth et al., 2009). An Indian series showed discordance between antemortem and postmortem diagnosis in 42% cases (Lanjewar, 2011). Russian authors reported that in 7% of cases HIV infection (!) was detected only postmortem (Berdnikov et al., 2011). Both false positive as well as false negative antemortem diagnoses are described (Martinson et al., 2007). Infections such tuberculosis, *Cytomegalovirus* and invasive mycoses are missed with the highest rate (Antinori et al., 2009; Beadsworth et al., 2009; Eza et al., 2006; Tang et al., 2006; Wilkes et al., 1988).

3.3 Current trends

The most notable changes described in reviewed series are the rise of tuberculosis infection and bacterial pneumonias for last 10 years (Fig. 3). Tuberculosis is often represented by generalized and disseminated forms. Bacterial infections still occur more frequently than other opportunistic infections in patients with HIV. Multiple infections with involvement of several organs are common.



Abbreviations: PCP, pneumocystic pneumonia; CMV, *Cytomegalovirus* infection; MAI, *Mycobacterium avium-intracellulare* infection; TB, tuberculosis; IFI, invasive fungal infections; Toxo, toxoplasmosis

Fig. 3. Major changing patterns of AIDS reported in retrospective studies.

Lungs and central nervous system are the most common targets for pathological processes. The incidence of pneumocystic pneumonia has declined significantly as a result of antiretroviral therapy and chemoprophylaxis. Rates of CMV infection also had been decreased, but not so markedly as pneumocystosis.

The possible concern of described results is that early autopsy series from our set represent high-income developed countries and the most recent series are from low- and middle-income countries. Therefore, it is more correct to report about emergence of HIV-related tuberculosis in developing countries than all over the world. Actually, in Western world (high-income model) tuberculosis spreads through HIV-infected cohort, while in Russia and India social conditions drives tuberculosis in neglected population (alcoholics, imprisons, homeless), that is superimposed by HIV. Contribution of non-HIV-related pathology in AIDS mortality depends on availability of HAART and, consequently, economical development of the country.

Finally, we may suppose that current trends in AIDS mortality for low- and high-income countries are different. Emergence of tuberculosis and high prevalence of bacterial infections are typical for Sub-Saharan Africa, South-East Asia and Eastern Europe. Growth of non-AIDS-related diseases is observed in USA and Western Europe.

4. Conclusion

Through the whole timeline of HIV epidemics significant differences in epidemiology contributed to evolution of disease. Thus, changing patterns of geographic distribution, modes of infection, spectrum of secondary diseases were widely described and explained. Since the first reports on AIDS autopsy has playing an important role in study of HIV infection. Autopsy series and case reports provided abundance of data on various aspects of AIDS. Soon after introduction of HAART large retrospective autopsy studies covering several thousand cases were published (Jellinger et al., 2000; Morgello et al., 2002; Neuenburg et al., 2002; Vago et al., 2002). Results of comprehensive post-mortem examinations were in concordance with data from numerous clinical studies declaring efficacy of therapy and marked reduction of mortality from AIDS (de Martino et al., 2000; Mocroft et al., 1998; Palella et al., 1998). HAART contributed the most important shift in the history of HIV epidemics. However, currently only 10% (roughly) of HIV patients globally are receiving ART (Brown et al., 2010). Moreover, rates of non-adherence to antiretroviral therapy has been shown to range from 33% to 88% (Mills et al., 2006). Access to antiretroviral therapy in developing high-burden countries is restricted and number of AIDS-related deaths in only Sub-Saharan Africa for the last 10 years has exceeded 10 million (UNAIDS, 2009).

The total number of HIV autopsies declined worldwide after the advent of combination therapy. It is thought, that recruiting of such sophisticated studies like autopsy series to analysis of morbidity and mortality trends is not reasonable. Instead of that new methods are established to assess mortality statistics in developing countries (Bhattacharaya & Neogi, 2008). Currently, the popularity of studies evaluating AIDS-related mortality by means of verbal autopsy is increasing (Bundhamcharoen et al., 2011; Lopman et al., 2010; Negin et al., 2010).

We believe that autopsy series represent most reliable sources in estimation of mortality trends. While in the early years of HIV epidemics autopsy function was largely scientific (e.g. recognizing and describing), nowadays the epidemiological data are of main value. Systematic retrospective study of autopsy series worldwide is a valuable tool that should contribute to the study of AIDS epidemics evolution.

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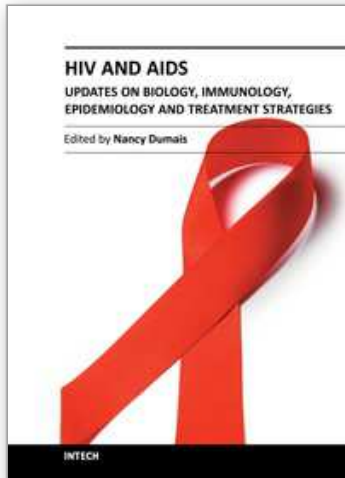
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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, “From the laboratory to the clinic,” and the second part, “From the clinic to the patients,” represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

How to reference

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