Annals of Parasitology 2019, 65(1), 3-17
doi: 10.17420/ap6501.178

Review articles

Immunomodulatory influence of HIV and EBV on *Helicobacter pylori* infections – a review

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ABSTRACT. *Helicobacter pylori* is a Gram-negative, microaerophilic rod colonizing the stomach mucosa. In most cases, the colonization of this organ is asymptomatic, while some people may develop diseases, including gastritis, peptic ulcers and gastric cancers. The infection caused by *H. pylori* is accompanied by the secretion of pro-inflammatory cytokines and the strong response of Th_1/Th_{17} cells. Because this bacterium colonizes more than half of the human population, co-infections with other pathogens are a relatively common phenomenon. One of such etiological factors are viruses that have an immunomodulatory effect on the infection caused by this microorganism. The relationship between *H. pylori* and HIV is antagonistic because there is an inverse relationship between the occurrence of this virus and the presence of *H. pylori*-dependent inflammations of the stomach. This is most probably caused by the HIV-related shift from a Th_1 to a Th_2 response and the reduction in Th_{17} cell counts. The reverse, synergistic interaction was demonstrated between *H. pylori* and EBV. Both of these pathogens are responsible for the recruitment of immune cells with a pro-inflammatory activity leading to the induction of gastric inflammation. The presence of the pro-inflammatory environment in the stomach supports the multiplication of both pathogens by maintaining *H. pylori* in the form of metabolically active, spiral forms and switching EBV from a latent into lytic phase. This review article discusses the epidemiology, pathophysiology and clinical consequences of *H. pylori* co-infection with HIV and EBV.

Key words: coccoid forms, *H. pylori*, immunomodulation, immunosuppression, inflammation

Helicobacter pylori is a Gram-negative, microaerophilic, flagellated rod colonizing the stomach mucosa of humans. This microorganism occurs naturally in a spiral form (live, culturable), while under conditions of increased environmental pressure it has the ability to transform into a coccoid form (viable but non-culturable, VBNC), a morphotype with a low metabolic activity [1]. It is estimated that over half of the human population (4.4 billion people) is colonized by *H. pylori*. The frequency of this process depends on many factors, i.e. the level of urbanization and sanitation, access to clean water or socioeconomic status. At the continental level, the highest rate of infection occurs in Africa (70.1%) and the lowest in Oceania (24.4%). Nigeria (87.7%), Portugal (86.4%), Estonia (82.5%), Pakistan (81%), and Kazakhstan (79.5%) are among the countries with the highest rate of infection. The lowest infection rates were recorded in Switzerland (18.9%), Denmark (22.1%), New Zealand (24%), Australia (24.6%), and Sweden (26.2%). The prevalence of *H. pylori* in the countries of Central and Western Europe is contained in average values, i.e. Germany (35.5%), the Czech Republic (41.2%), France (46.9%), and Poland (66.6%) [2]. These discrepancies in the prevalence of *H. pylori* between the countries of Central and Western Europe are most likely caused by differences in the socio-economic status, because a high level of poverty, overcrowded living conditions and low personal hygiene are independent factors promoting *H. pylori* infections [3–8].

Colonization of the stomach by *H. pylori* most often takes place in childhood and persists throughout life in the absence of appropriate eradication therapy [9,10]. In most cases, colonization of this organ is asymptomatic, but in some cases diseases may develop, including

gastritis, peptic ulcers, gastric cancers and mucosa associated lymphoid tissue (MALT) lymphomas [11–14]. The acute phase of infection is associated with an intense inflammation of the gastric mucosa. This process is accompanied by an increased secretion of pro-inflammatory cytokines and the recruitment of various types of immune cells, i.e. neutrophils, macrophages, dendritic cells, B and T cells [15]. Such environment is dominated by the presence of pro-inflammatory cytokines (IL-2, IL-6, IL-12, IFN-γ, TNF-α), which influences the shift of lymphocyte subpopulation towards proinflammatory Th_1 cells [16,17]. In addition, the presence of anti-inflammatory cytokine TGF-β may ultimately affect the exacerbation of inflammatory reactions. This phenomenon is determined by the ability of this cytokine to stimulate the recruitment of both Th_{17} cells (strong pro-inflammatory activity; secretion of IL-17A, IL-17F, IL-21, IL-22) and Treg cells (strong anti-inflammatory activity; secretion of IL-10 and TGF-β). The presence of IL-6, produced intensively during the infection caused by *H. pylori*, modulates the activity of TGF-β and contributes to the formation of Th_{17} but not Treg cells. The intensified recruitment of Th_1 and Th_{17} cells favors their hyperactivity and may lead to the destruction of gastric tissue in reactions directed against this microorganism. Despite the strong activation of the immune system, the infection caused by *H. pylori* can last for many years, often even all life [16,18, 19].

Because *H. pylori* colonizes more than half of the human population, co-infections with other pathogens are a relatively common phenomenon. One of them are parasites, while the main mediator of the response to the ongoing infection is the host's immune system. Protozoa, which promote the formation of type 1 immune response (Th_1 cells and classically activated macrophages, CAM), increase the intensity of inflammation and, therefore, may lead to aggravated gastric lesions. Helminths are responsible for the development of type 2 immune response (Th_2 cells and alternatively activated macrophages, AAM), which determine the reduction of host hyperresponsiveness and exert a regenerative effect on the mucous membranes of the gastrointestinal tract [20–23], reviewed in [24].

Viruses are another important pathogens, besides parasites, able to co-infect humans together with *H. pylori*. For many of them, the ability to modulate host's immune system has been demonstrated, which may affect the functioning of this bacterium and *H. pylori*-depend inflammation of the gastric mucosa.

The aim of this review is to present information about the frequency of *H. pylori* co-infections with two viruses with high immunomodulatory activity, human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV), and their effect on the course of infection caused by this microorganism.

HIV

The global HIV pandemic, after thirty years since the virus was discovered, still remains valid. It is estimated that over 78 million people have been infected with this virus, of which 36 million currently live with HIV [25]. The HIV epidemic originated during zoonotic infections caused by simian immunodeficiency viruses (SIV). Bushmeat hunters were most likely the first infected group of people who contributed to the spread of the virus to the rest of the population [26]. A key feature of infection caused by HIV is a decrease in the amount of $CD4^+$ T lymphocytes. Because these cells have a central regulatory role in the proper functioning of the immune system, a reduction in their amount contributes to significant defects in the cellular and humoral antimicrobial response [27]. When the amount of $CD4^+$ T lymphocytes drops below 200/mm^3, acquired immunodeficiency syndrome (AIDS) develops, which is associated with a dynamic increase in viral load, drastic reduction in $CD4^+$ T lymphocytes and decrease in immunity of infected persons [28]. This condition is conducive to the emergence of opportunistic infections caused by, among others, *Pneumocystis carinii*, *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*, Cytomegaloviruses, Adenoviruses, Herpes simplex viruses and *Candida albicans* [29,30].

The factor that significantly reduced the mortality rate of people suffering from HIV and improved the quality of their lives was the introduction of anti-retroviral therapy (ART). Compounds used during this procedure interfere with various key HIV-related processes by inhibiting viral enzymes (reverse transcriptase, integrase, protease) and blocking the entry into the interior of eukaryotic cells [31]. Therapy with the use of these medications has evolved over the years and therefore three periods are distinguished: pre-HAART (highly active antiretroviral therapy, 1993–97), early HAART (1998–2003) and contemporary HAART (2004–present); among

which the latter is the most effective [25]. Despite the high efficiency of ART, drugs used are unable to completely eliminate HIV from the infected person's body. This is most likely caused by the existence of additional reservoirs of this virus, which are long-lived, latently infected resting $CD4^+$ T lymphocytes and monocytes/macrophages. In addition, this virus can also be found in the tissues of the digestive tract and central nervous system [32–34].

Frequency of *H. pylori* and HIV co-infection

The risk factors for the acquisition of *H. pylori* and HIV are different. For the first etiological factor, the main ways of spreading are gastro-oral and fecal-oral pathways; HIV, on the other hand, is spreading by sexual intercourses, contaminated body fluids or transplancentally [35–38]. Therefore, the presence of any of these pathogens should not affect the frequency and course of infection caused by the latter. A review of literature data, however, shows a different relationship [39–45].

In many articles, there was an inverse correlation between the incidence of *H. pylori* and HIV, especially in patients with $CD4^+$ T lymphocytes counts below the 200 cell/mm^3 threshold [39–45]. In two studies, the existence of such a dependence was noticed, although the differences between the studied groups were insignificant; *H. pylori* prevalence in patients without HIV infection (HIV^-) and with HIV infection (HIV^+) was estimated at 49.5% vs 41.1% [40] and 87.3% vs 73.1% [42], respectively. Eberhardt et al. [43] found a bigger difference, with the prevalence of *H. pylori* in HIV^- and HIV^+ counted for 87.3% vs. 56.2%, respectively. Fialho et al. [39] determined that the frequency of *H. pylori* in HIV-infected patients was almost twice lower (75.2% vs. 37.2%). In addition, in people with $CD4^+$ T lymphocytes >200 cells/mm^3 this frequency was higher (46.3%) than in patients with ≤200 cells/mm^3 (28.8%) [39]. A similar frequency of infection was shown by Lv et al. [44], in HIV^-Hp^+ it counted for 44.8%, and in HIV^+Hp^+ 22.1%. Here also the existence of lower prevalence of *H. pylori* in patients with lymphocytes ≤200 cells/mm^3 (29.2% vs 14%) was noticed. Mach et al. [41] observed a similar trend, i.e. the occurrence of *H. pylori* was confirmed in 69%, 72% and 40% of HIV^-Hp^+ patients, HIV^+Hp^+ $CD4^+$ >200 cells/mm^3 and $CD4^+$ ≤200 cells/mm^3, respectively. The study of Cacciarelli et al. [45] showed the prevalence of *H. pylori* in the same patient categories at 63%, 69% and 13%. On this basis, the conclusion was drawn that the incidence of *H. pylori* decreases with decreasing amounts of $CD4^+$ T lymphocytes [39,41–46]. Because the presence of this bacterium exerts a stimulatory effect on $CD4^+$ T lymphocytes in HIV^+Hp^+ people, a higher level of them was observed, which in turn correlated with the lower load of virus [40,43,46]. This suggests that *H. pylori*-dependent recruitment of lymphocytes may increase the antiviral activity of immune cells during HIV infections.

Immunological consequences of *H. pylori* and HIV co-infection

Numerous scientific reports have recognized the immunomodulatory effect of HIV against the activity of *H. pylori* and associated with this bacterium gastric mucosa pathologies [25,41,44,45, 47]. In these studies, it was noted that the presence of HIV reduces the incidence of active gastritis and/or peptic ulcer disease in individuals infected simultaneously by *H. pylori*. The frequency of gastritis detection in HIV^+Hp^+ patients was almost twice lower than in HIV^-Hp^+ patients (37% vs 63%) [47], and gastric ulcer disease was 4-fold [44] or 8-fold lower (HIV^- vs AIDS) [45]. In a recent study, Radovanović et al. [25] analyzed the correlation between the prevalence of gastric pathologies and HAART. It was observed that in the pre-HAART patient group the severity of gastritis was lower (16% without gastritis, 66.7% mild gastritis) than those treated with the early HAART (62.5% mild gastritis, 25% moderately advanced gastritis) or modern HAART (50% mild gastritis, 37.5% moderate advanced gastritis, 12.5% advanced gastritis). These results may suggest that increased effectiveness of antiviral therapies against HIV has contributed to a stronger reduction in virus number and more advanced *H. pylori*-dependent pathological changes in the stomach [25]. On this basis, the authors of the papers concluded that *H. pylori* to trigger inflammation of the stomach mucosa requires a functional immune system of the host [25,41,44,45,47].

Hypotheses explaining *H. pylori*-HIV interactions

Currently, there are two hypotheses explaining

the existence of an inverse correlation between the prevalence of HIV and *H. pylori*.

The first one suggests a high level of antibiotic use in HIV^+ people in purpose of protection against potential opportunistic infections. Frequent consumption of antibiotics may lead to incidental eradication of *H. pylori* [48]. It seems, however, that this model is not reliable, because although such a situation is not impossible, there is a marginal chance that this phenomenon contributes to such significant differences in the prevalence of *H. pylori* between groups of HIV^+ and HIV^- patients. Moreover, nowadays, the high level of antibiotic resistance of *H. pylori* strains (including two or three antibiotics at the same time) is observed all over the world, so the use of monotherapy seems insufficient to achieve full eradication of this bacterium [49–52]. This model was further indirectly refuted by Nkuize et al. [53], who showed that HIV^+ patients were more likely to have strains of *H. pylori* resistant to levofloxacin, metronidazole or several antibiotics (clarithromycin and metronidazole, levofloxacin and metronidazole, or all three antibiotics). Therefore, *H. pylori* co-infection with HIV seems to be responsible for spreading of antibiotic resistance among the strains of this bacterium rather than eradicating this microorganism.

The second hypothesis mentions that in the course of acute inflammatory processes many cells of the gastric mucosa are destroyed and nutrients released from them are collected then by *H. pylori*. Because in people with HIV infection, especially with AIDS, the destruction of the stomach is reduced, it may limit the amount of substances available for *H. pylori* and lower the prevalence of this bacterium during HIV infection [54]. This is consistent with reports of preferential colonization of damaged stomach mucosa sites by *H. pylori* [55]. This model takes into account that properly functioning immune cells through activity directed against *H. pylori* may contribute to the destruction of stomach epithelial cells and the release of nutrients accumulated there. However, this bacterium is able to obtain the necessary substances from the stomach mucosa through the production of

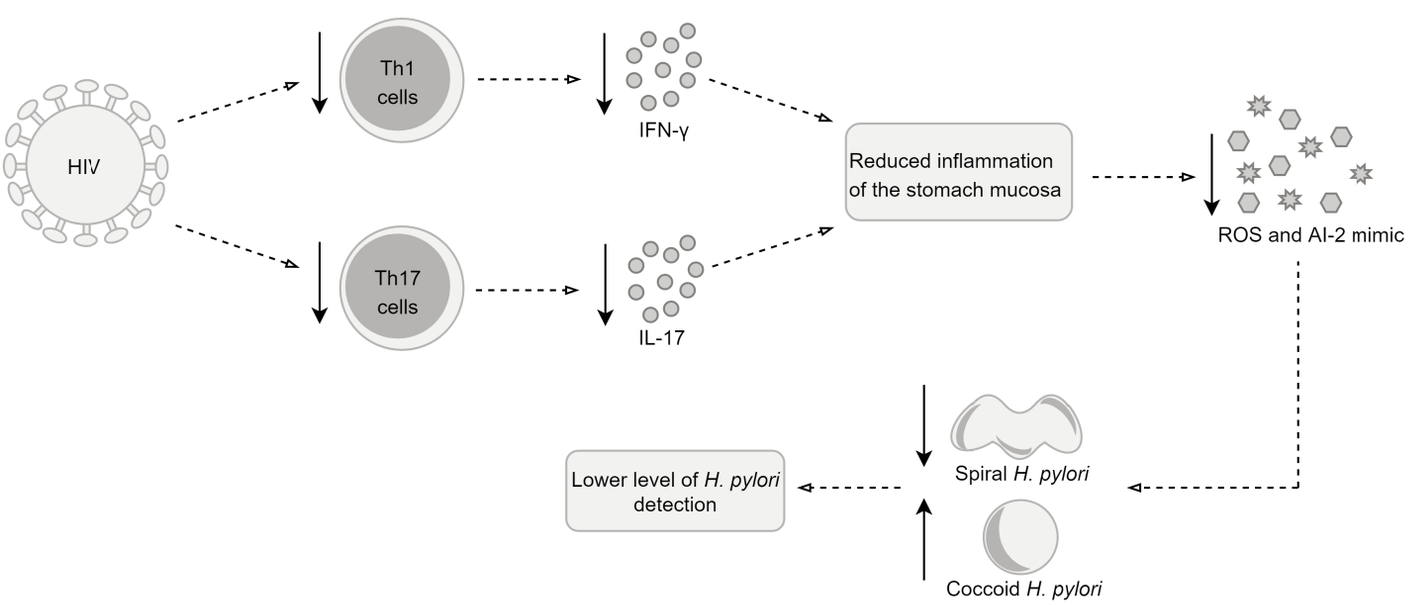

Fig. 1. Inverse correlation between the occurrence of HIV and *H. pylori* – the morphological conversion hypothesis. As a result of HIV infection, there is a decrease in the number of Th_1 and Th_{17} cells and secretion of IFN-γ and IL-17, respectively. The reduction in the production of these pro-inflammatory cytokines correlates with a lower intensity of gastric inflammatory processes and a reduced level of ROS and AI-2 mimics. Lower secretion of these factors correlates most probably with a decreased spiral subpopulation of *H. pylori* and a simultaneous increase in the subpopulation of spherical forms. The reduced metabolic activity of coccoid forms may contribute to a lower level of *H. pylori* detection using standard detection methods, but not necessarily with the actual reduction of its prevalence.

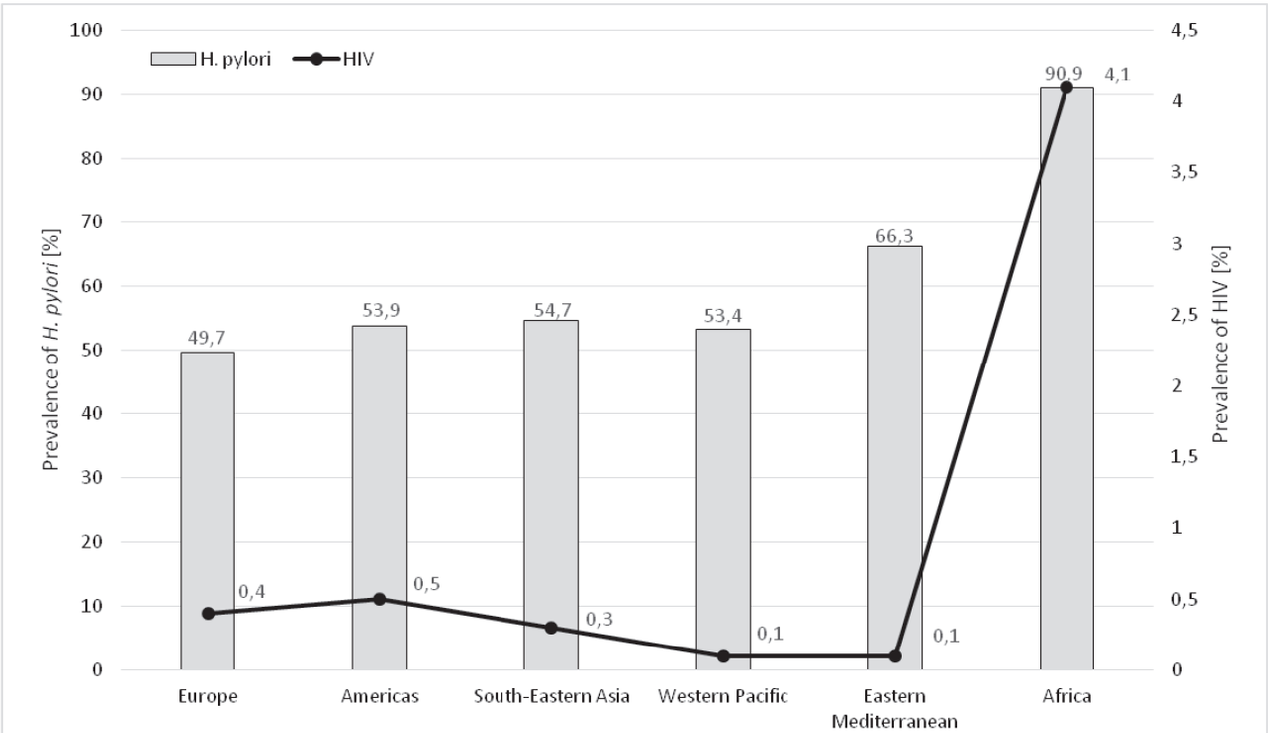

Fig. 2. Lack of relationship between a global *H. pylori* and HIV distribution.
In order to compare the global distribution of the two pathogens, data from Hooi et al. [2] have been modified according to [80] and presented as: Europe (Europe + Central Asia + Greenland), Americas (Greenland has not been counted here), South-Eastern Asia (South-Eastern Asia, India and Nepal), Western Pacific (Eastern Asia + Oceania), Eastern Mediterranean (Western Asia, Iran, Lebanon, Pakistan, Egypt, Libya and Tunisia) and Africa (Egypt, Libya and Tunisia have not been counted here).

virulence factors, i.e. vacuolating cytotoxin A (VacA), cytotoxin-associated gene A (CagA), neutrophil-activating protein A (NapA) or HtrA protease that exert direct, destructive effects on this tissue, regardless of the presence of immune cells [56–59]. Therefore, it seems that the model of nutritional limitations caused by HIV is too simplified.

Based on a review of literature data, the authors of this review suggest the existence of an alternative model explaining the antagonistic relationship between the occurrence of HIV and *H. pylori* (Fig. 1).

In people infected with *H. pylori*, a mixed Th_1/Th_{17} response develops, which is associated with a strong activation of the immune system and destruction of local stomach tissues [60]. The main factors involved in the promotion of *H. pylori*-dependent inflammation of the gastric mucosa are pro-inflammatory cytokines IL-8 [61], IL-17A [60–65], INF-γ [60,62–65] and TNF-α [62]. Secretion of these cytokines and recruitment of Th_1 and Th_{17} cells is essential for the fight against *H. pylori*, while most often it is insufficient to effectively eradicate this bacterium [16]. Interestingly, the number of lymphocytes producing the above-mentioned cytokines is positively correlated with *H. pylori* density. Therefore, it seems that the activity of Th_1/Th_{17} cells and the generation of a pro-inflammatory environment favor the survival of *H. pylori* in the stomach [60,61,63].

In the study, Ismail et al. observed that mammalian epithelial cells in response to factors destructing tight junctions (including pore-forming toxins) secreted substances with structural homology with autoinducers-2 (AI-2), i.e. signaling molecules responsible for an intermicrobial communication [66]. For *H. pylori* AI-2 are chemorepulsive signals, which means that they promote negative chemotaxis against the source of these signals [67,68]. It is also suggested that AI-2 may play a key role in keeping these bacteria in a spiral form and/or transforming from a spherical into a spiral form [69]. The *H. pylori* chemorepulsive movement has also been demonstrated against

sources of oxidative stress, including reactive oxygen species (ROS) [70]. On this basis, it can be concluded that inflammation of the gastric mucosa, through the generation of AI-2 mimic and ROS, maintains *H. pylori* in a state of live, metabolically active spiral forms.

Numerous scientific reports have highlighted the immunomodulatory properties of the HIV. It was noticed that as a result of infection caused by this virus the Th_1 response is shifted to Th_2 type [71–74] and the Th_{17} cells number is decreased [75]. The enhancement of the polarization of Th_2 cells by HIV is particularly evident in the case of co-infections with helminths, which also determine the recruitment of this subpopulation of immune cells. The co-occurrence of HIV with these parasites correlated with the higher plasma viral load, and anti-parasitic therapy eliminated this effect [76,77]. It was observed that the process of shifting response from the Th_1 to the Th_2 type and reducing the number of Th_{17} cells is accompanied by a decrease in secretion of IFN-γ and IL-17, two key cytokines in the *H. pylori*-dependent generation of the gastric inflammation [71–75]. Such a change in the activity of the immune system may have a direct effect on the physiology of *H. pylori* and reduce the frequency of spiral forms of this bacterium with the growing appearance of spherical forms. This is consistent with the observations showing the inverse correlation between the prevalence of *H. pylori* coccoid forms and the exacerbation of destructive changes in the gastric mucosa [78,79].

Indirect proof of the absence of a reverse correlation between prevalence of *H. pylori* and HIV provides an analysis of the global distribution of these pathogens [2,80]. Comparing the prevalence of these etiological factors in the world, the authors of this article did not observe any relationship between the occurrence of HIV and *H. pylori*. Although, for both of them the highest prevalence is noticed in Africa (4.1% and 90.9%, respectively), the frequency is variable in other parts of the world (Fig. 2). For example, the lowest prevalence of *H. pylori* is observed in Europe (49.7%), while in the case of HIV it is relatively high being fourfold higher (0.4%) than for the Western Pacific (0.1%) and Eastern Mediterranean (0.1%) regions (Fig. 2). Despite the same prevalence of HIV in these areas, *H. pylori* is detected at a different rate of 53.4% and 66.3%, respectively (Fig. 2). On this basis, it appears that the relationship in the global distribution between *H. pylori* and HIV does not exist.

To sum up, based on the above considerations, the existence of an antagonistic relationship between HIV and *H. pylori* is suggested (Fig. 1). In the course of infection caused by HIV, a strong recruitment of Th_2 cells and reduction of Th_1/Th_{17} cells occur. This phenomenon is accompanied by a decrease in the pro-inflammatory response against *H. pylori* and the intensity of gastritis, and thus lower generation of ROS and AI-2 mimic. Lower secretion of these factors correlates most probably with a decreased spiral subpopulation of this bacterium and a simultaneous increase in the subpopulation of spherical forms – viable but non-culturable. The reduced metabolic activity of these morphological forms may contribute to a lower level of *H. pylori* detection using standard detection methods, but not necessarily with the actual reduction of its prevalence. Therefore, we propose to name this model as a „Morphological conversion hypothesis".

EBV

EBV (Herpesvirus-4, HHV-4) is a dsDNA virus that belongs to the γ-herpesvirus family. EBV infections occur with an 80–100% incidence among adults around the world, and the first contact with this pathogen occurs in early childhood. The virus spreads through droplets, by contact with the saliva of the infected person. After contact with secretions, epithelial cells of the nasopharynx are infected. Then, the virus spreads to lymphoid tissues where it infects B lymphocytes [81–84].

During infection, EBV remains lifelong in the latent phase in B cells. Due to this localization, this virus has the ability to initiate various lymphoproliferative diseases (Burkitt's lymphomas, Hodgkin's lymphomas, diffuse large-B cell lymphomas), as well as mononucleosis, autoimmune diseases and cancers (nasopharynx and stomach) [81,85–90]. Most of the infections caused by EBV are asymptomatic, while the manipulation of host cell physiology during the latent phase may lead to induction of carcinogenesis [91]. The EBV potential to induce stomach tumors is caused by the high morphological similarity between lymphoepithelioma-like carcinoma (LELC) and undifferentiated nasopharyngeal carcinoma (UNPC) [92, 93]. For this reason, determining the prevalence of EBV and *H. pylori* co-infection and the potential interaction between these etiological factors seems highly significant.

Immunological consequences of *H. pylori* and EBV co-infection

Due to the high frequency of colonization of the human population by both pathogens, often reaching 80–90% in some populations, the majority of research focuses on the pathophysiological effects of *H. pylori* and EBV co-existence.

In the analysis of biopsies taken from people with various gastrointestinal diseases, Shukla et al. noted that the frequency of EBV DNA isolation was significantly higher in patients with gastric cancers (GC, 90%) and gastric ulcers (PUD, 70%) than in those with non-ulcer dyspepsia (NUD, 37%) [94]. In addition, GC and PUD subjects had a higher copy of the virus (1329.2 copies/10^6 eukaryotic cells and 754 copies/10^6 eukaryotic cells, respectively) compared to NUDs (86.8 copies/10^6 eukaryotic cells). It has also been observed that co-infection increase both the number of virus copies (EBV^+Hp^- 177.8 copies/10^6 eukaryotic cells vs EBV^+Hp^+ 519.4 copies/10^6 eukaryotes), as well as the amount of *H. pylori*, calculated by specifying the number of *ureA* copies (EBV^-Hp^+ 1329 copies/10^6 eukaryotic cells vs EBV^+Hp^+ 2500 copies/10^6 eukaryotic cells). These results suggest that the presence of one of these etiological factors exerts a beneficial effect on the multiplication of the other and *vice versa* [94] (Fig. 3). The mechanisms controlling this interaction are not known. One of the suggested factors related to the transition of EBV from the latent to the lytic phase is monochloramine (NH_2Cl), which is formed in the *H. pylori*-dependent manner during the inflammation of gastric mucosa. This was

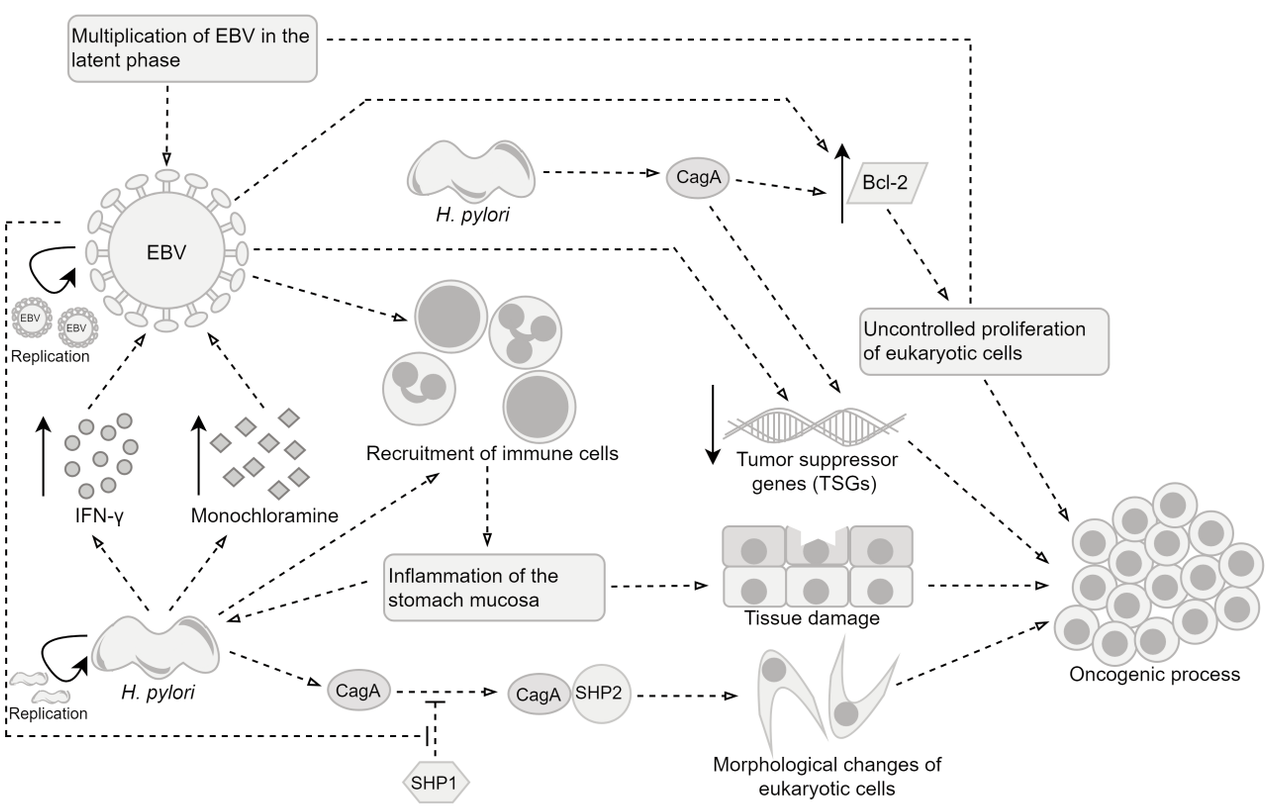

Fig. 3. Synergistic relationship between EBV and *H. pylori*.
During the infection caused by both EBV and *H. pylori*, immune cells associated with pro-inflammatory activity are recruited leading to the induction of gastric inflammation. Promotion of this process indirectly influence the induction of tumorigenesis and exert a pro-proliferative effect on *H. pylori*. As a result of the intensive multiplication of this bacterium, there is an increased secretion of IFN-γ and monochloramine, which promote EBV proliferation and initiate the shift of this virus from the latent to the lytic phase. EBV and *H. pylori* $CagA^+$ strains are able to immortalize and induce uncontrolled proliferation of eukaryotic cells by promoting high concentrations of anti-apoptotic Bcl-2 protein. This process promotes the multiplication of the virus, found inside the eukaryotic cells, which in turn determines an increase in CagA-dependent promotion of oncogenesis. This phenomenon is related to silencing of the eukaryotic factor with anti-CagA activity-SHP1, increasing the amount of CagA-SHP2 complexes and boosting the pro-oncogenic activity of this protein. In addition, EBV and *H. pylori* $CagA^+$ strains reduce the amount of tumor suppressor genes (TSGs), thus indirectly leading to the promotion of tumorigenesis.

demonstrated by the action of NH_2Cl on AGS cell line infected latently by EBV, resulting in a massive entry of the virus into the lytic phase [95]. The second factor potentially involved in the promotion of EBV proliferation is the *H. pylori*-dependent stimulation of IFN-γ secretion, one of the key pro-inflammatory cytokines arising in the course of gastric inflammation. It was noticed that the level of this cytokine in the plasma of patients with gastric cancers was positively correlated with the degree of reactivation of the virus [96]. On the other hand, EBV has also been shown to be able to support *H. pylori* multiplication [94]. The reason for this mechanism has not been characterized. Co-infection with both etiological factors contributes to the intensification of the immune cells influx and the secretion of pro-inflammatory cytokines in the gastric mucosa. It seems, therefore, that an increase in the density of *H. pylori* localized in the stomach occurs through intensified activity of Th_1/Th_{17} cells and generation of the pro-inflammatory environment (Fig. 3).

Studies of Cárdenas-Mondragón et al. focused on establishing the relationship between both the occurrence of a single infection caused by *H. pylori* or EBV and co-infections with severity of gastric pathologies [97,98]. The first study determined seroprevalence against EBV and *H. pylori* in patients with stomach diseases. Special attention was paid to the analysis of people with carcinogenesis processes. It was found that anti-EBV antibodies were positively correlated with the presence of premalignant lesions and intestinal-type cancers, whereas anti-*H. pylori* antibodies were associated with the presence of premalignant lesions and diffuse-type cancers. Attention was drawn to the existence of a relationship between the exacerbation of gastric mucosa inflammation and the increased degree of EBV reactivation, suggesting a potential contribution of pro-inflammatory products in initiating the transition of this virus to the lytic phase [98] (Fig. 3). Observations on pro-oncogenic potential of *H. pylori* and EBV are consistent with Szkaradkiewicz et al. [99] reports, who proved that in the course of infection caused by these pathogens there is an increased expression of the eukaryotic anti-apoptotic factor Bcl-2, which may contribute to the development of the carcinogenesis (Fig. 3). In the second study of Cárdenas-Mondragón et al., children with abdominal pain were analyzed [97]. It has been shown that the infection caused by one pathogen was associated with the benign or moderate recruitment of mononuclear cells (EBV^+: 97.8% mild, 0% advanced; Hp^+: 66% mild, 7.5% advanced), and co-infection significantly exacerbates this process (EBV^+Hp^+: 60% mild, 16.8% advanced). Similar observations have been made for polymorphonuclear immune cells. In this case, the infection with a single etiological factor was not responsible for the recruitment of this type of cells or determined only its mild course (EBV^+: 94.4% none, 1.1% moderate advanced; Hp^+: 60.4% none, 5.7% moderate advanced), while the presence of both pathogens intensified this process (EBV^+Hp^+: 58.4% none, 21.6% moderate advanced). Furthermore, the presence of *H. pylori* strains producing CagA ($CagA^+$), the toxin responsible for the cytoskeleton rearrangements and the stimulation of the oncogenesis process, were associated with the highest intensity of immune cells influx [97].

There are scientific reports demonstrating the significance of CagA as a modulator of EBV-*H. pylori* interaction [100,101]. CagA exists in two forms, i.e. phosphorylated and non-phosphorylated. Both forms have a pro-inflammatory effect on eukaryotic cells, whereas for the phosphorylated form high significance in initiating oncogenesis is suggested. This mechanism is related to the ability of the phosphorylated CagA to form complexes with the eukaryotic factor SHP2, and thus the process of initiating inflammation and morphological changes in host cells, so-called a hummingbird phenotype [102] (Fig. 3). SHP1 is a eukaryotic factor regulating CagA activity, contributing to the protection against the destructive effect of this protein by the process of dephosphorylation and reduction of the CagA-SHP2 formation. In *in vitro* conditions, it was observed that in EBV-infected eukaryotic cells the SHP1 promoter undergoes hypermethylation, thereby reducing the amount of SHP1 and the degree of CagA dephosphorylation, which in turn increases the pro-oncogenic activity of this bacterial protein [100] (Fig. 3). Another study found that the co-existence of *H. pylori* with EBV increased the pro-carcinogenic potential of the latter, and the main mediator of this interaction was CagA. EBV contributed to the methylation of tumor suppressor genes (TSGs) and this ability was further enhanced by the presence of CagA, secreted by *H. pylori*. The phenomenon of a strong reduction in TSGs activity promotes the uncontrolled proliferation of virus-containing cells, conditioning its faster multiplication, and increases the chances of developing

tumors [101] (Fig. 3). These studies show that both EBV and *H. pylori*, in the epigenetic modification processes, support each other's survival capabilities in the host and the potential to induce pathological processes, including the ability to cause inflammations and cancers.

To sum up, based on the above considerations, it is suggested that there is a synergistic relationship between EBV and *H. pylori* (Fig. 3). During the infection caused by both EBV and *H. pylori*, immune cells associated with pro-inflammatory activity are recruited leading to the induction of gastric inflammation. What's more, the co-infection of both pathogens is associated with exacerbation of this phenomenon. Increased secretion of pro-inflammatory cytokines is most likely a stimulant for *H. pylori* proliferation and transition of EBV from the latent to the lytic phase. Intensive proliferation of both etiological factors further strengthens the induction of gastric inflammation-dependent pathologies. *H. pylori* CagA$^+$ strains are characterized by the highest level of synergistic activity with EBV in promoting pathophysiological changes, which is dependent on the ability of CagA to initiate the immortalization and increased proliferation of eukaryotic cells. Uncontrolled divisions of host cells support the multiplication of latent EBV, which in turn determine the increase in the intensity of CagA-dependent oncogenesis promotion. This phenomenon is associated with hypermethylation of SHP1 by EBV, increase in the amount of CagA-SHP2 complexes and promotion of the pro-oncogenic activity of this protein. This model suggests that the interaction between *H. pylori* and EBV has the character of positive feedback.

Summary

H. pylori colonizes over half of the human population. For this reason, co-infections with other pathogens occurs relatively frequently. One of these pathogens are viruses, including HIV and EBV.

The key feature of infections caused by HIV is a decrease in the number of CD4$^+$ T lymphocytes and, what is associated with this, a decrease in the activity of the immune system. In many scientific reports, attention was drawn to the existence of an inverse correlation between the occurrence of HIV and *H. pylori*, especially in people with AIDS. In addition, the presence of HIV significantly reduces the incidence of *H. pylori*-related gastrointestinal diseases. On this basis, the conclusion was formulated that this bacterium to cause inflammation of the gastric mucosa requires the presence of a functional host immune system. The hypotheses explaining this phenomenon mention a high degree of antibiotic use in HIV$^+$ patients and a reduction in the immune-dependent breakdown of eukaryotic cells that are the source of nutrients for this bacterium. An alternative hypothesis, based on our own considerations, suggests that by a shifting the Th_1 response towards Th_2 type and reducing the number of Th_{17} cells the frequency of the metabolically active, spiral *H. pylori* forms decreases with a simultaneous increase in the amount of coccoid forms. The presence of these morphological forms may decrease the effectiveness of *H. pylori* detection using routine diagnostic methods, but does not necessarily correlate with the actual reduction of the prevalence of this microorganism („Morphological conversion hypothesis") (Fig. 1).

In the course of the host infection, EBV remains in the latent phase in B cells, which is related to the ability to initiate various lymphoproliferative, autoimmune and oncogenic diseases. It was noticed that there is a positive correlation between *H. pylori*-EBV co-infection and the severity of gastrointestinal diseases (Fig. 3). This mechanism is most likely dependent on the ability of these pathogens to intensify the influx of immune cells, increase the secretion of pro-inflammatory cytokines and promote their own multiplication. Observations of many scientific centers have shown the pro-oncogenic potential of these pathogens, especially in the course of co-infection. This phenomenon is related to the induction of uncontrolled proliferation of eukaryotic cells and the reduction of TSGs activity. The interaction between *H. pylori* and EBV has the character of positive feedback.

This article demonstrates the immuno-modulatory effect of HIV and EBV on the course of infection caused by *H. pylori*. Based on the literature review, it is concluded that the co-existence of *H. pylori* with other pathogenic agents may diametrically shape the pathophysiology of this bacterium. Therefore, a holistic view of disease processes taking place in the human body is postulated.

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Received 28 September 2018
Accepted 05 January 2019