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THE BEST STRATEGY FOR *HELICOBACTER PYLORI* ERADICATION IN PEOPLE LIVING WITH HIV IN THE ERA OF ANTIBIOTIC RESISTANCE

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Abstract – Currently, there is a global increase in *Helicobacter pylori* (*H. pylori*) antimicrobial resistance with an increase in parallel of *H. pylori* treatment failure in the general population in several regions. At the same time and in relation to the pandemic of HIV infection, little is presently known on *H. pylori*-HIV co-infected people who receive *H. pylori* treatment based on international guidelines for the general population. We believe that this HIV co-infected population is a special niche because it harbors strains with multiple resistances to antibiotics compared to the general population; hence this co-infected population should receive specific recommendations in relation to their condition. Therefore, based on current literature, we propose a "best approach" to offer optimal efficacy of *H. pylori* treatments in people living with *H. pylori* and HIV co-infection.

Keywords: HIV, Helicobacter pylori, Antibiotic resistance, Eradication, Bismuth, Microbiota, Coinfection, Drug interaction, Best strategy.

INTRODUCTION

Globally speaking, there has been an increase in *Helicobacter pylori (H. pylori*) antimicrobial resistance leading to more *H. pylori* treatment failures in several regions. The drop in efficacy is gradual across time in the general population[1,2]. By contrast, there is presently little data concerning *H. pylori* treatment in *H. pylori*-HIV co-infected people and, as a result, they are treated based on guidelines devoted to the general population. These *H. pylori*-HIV co-infected people are mainly characterized by immune dysfunction, more frequent infections (opportunistic or non-opportunistic) and exposition to antibiotics, and more comorbidity treatments than the general population. Thus, we recently found an increase in antibiotic resistance (single and multiple) of *H. pylori* strains isolated from people living with HIV (PLWH) in comparison to HIV-negative people. Furthermore, this greater frequency of antibiotic resistance of *H. pylori* strains isolated from PLWH persists with time. Consequently, we observed a failure rate for empirical *H. pylori* treatment of 25% in *H. pylor*i-HIV co-infected people *vs.* 9.4% in the HIV-uninfected people. This lower efficacy of all empiric treatments is in part related to the high rate of antibiotic resistance of *H. pylor*i strains isolated among *H. pylo-*

*r*i-HIV coinfected people who are treated similarly to the general population. Furthermore, issues like drug-drug interactions in *H. pylor*i-HIV co-infected people receiving drugs against co-morbidities and HIV infection are observed. It is important to note that the main threats to *H. pylori* eradication are antibiotic resistance and treatment compliance[3-8].

We sought to propose a strategy optimizing the first-line therapy against *H. pylori* among PLWH based on a literature review.

For the review, a PubMed search was performed using the keywords "*Helicobacter pylori*" or *H. pylori* treatment", "eradication failure", "HIV co-infection", "antiretroviral interactions", "microbiota in *Helicobacter pylori* or HIV", and "therapy adherence or compliance" in literature on the target topics between January 2008 and March 2021. An additional manual search on "consensus guidelines" was carried out by means of internet sites.

ANTIMICROBIAL SUSCEPTIBILITY TESTING-GUIDED THERAPY

As an infectious disease, antimicrobial susceptibility testing (AST) performed either by antibiogram, PCR, or next-generation sequencing allows individualization of the *H. pylori* eradication treatment. Accordingly, AST-guided *H. pylori* therapy is associated with a response rate of >90% in intention-to-treat (ITT) in the general population. A meta-analysis of 5 randomized control trials including 701 patients compared AST-guided triple therapy *vs.* empiric therapy. The eradication rates in ITT were 85.4% and 71.5%, respectively (RR 0.84; 95% CI [0.77-0.90], $p<0.00001$). When the local prevalence of clarithromycin (CLA) resistance is above 15%, the recommendation is to treat *H. pylori* infection based on AST, if possible, with an antibiogram. The economical cost of guided therapy is cheaper than that of empiric therapy[9]. The use of an antibiogram offers different therapeutic regimens that include:

– CLA-susceptible strains: standard triple therapy with amoxicillin (AMX), CLA, proton pump inhibitor (PPI) for 14 days.
– CLA-resistant: triple therapy with AMX, metronidazole (MTZ), PPI for 14 days.
– MTZ- and CLA-resistant: triple therapy AMX, levofloxacin (LEVO), PPI for 14 days.
– The overall eradication rate of >90% can be achieved unless parameters like compliance or drug metabolism contribute to a drop in the eradication rate.
– MTZ-, CLA- and MET-resistant: bismuth quadruple therapy (BQT) for 10 to 14 days or optimized bi-therapy for 14 days, or rifabutin-based triple therapy[1,10]. This latter therapy required caution in PLWH because tuberculosis (TB) is common in this population (see the next paragraph).

In a prospective study[8], a subgroup of 42 *H. pylori*-HIV co-infected patients treated after AST (based on biopsies from both the antrum and corpus)-guided triple therapy against *H. pylori* for 14 days, achieved an ITT eradication rate of 38/42 (90.5%) similar to the control (91%). Before the triple therapy prescription, a systematic check for interaction between drugs (using internet sites) is considered important. It led to an antiretroviral (ARV) switch in 9 patients before initiating the anti-*H. pylori* treatment. That allowed avoiding either the prescription of a suboptimal dose of PPI or antibiotic or concomitant use of ARV that can induce a sub/supra-therapeutic ARV dose leading to viremia rebound or toxic effect, a factor contributing to poor adherence. In this strategy, we used potent PPIs like esomeprazole (40 mg twice a day)[1,11]. Three out of 4 failures were due to the patient's decision (rather than the physician's advice) to reduce the pill dose or frequency because of adverse events. Nevertheless, at treatment initiation, the referent physician must provide the patient with explanations. Those explanations would be provided using support-writing material, presenting the treatment schedule, dose, daily frequency, and duration, and using multimedia support contact during the treatment. We previously named this approach by the acronym "AISR": Antibiogram-drug Interaction-Support material/multimedia-Referent physician: that integrates AST, drug pharmacology, and patient support to obtain optimal adherence supported by the physician (Figure 1).

Another cost saved by AST is the reduction in *H. pylori* eradication attempts, resulting in the consumption of fewer antibiotics, and therefore, preserving the diversity within the microbiota (see the section on the microbiota).

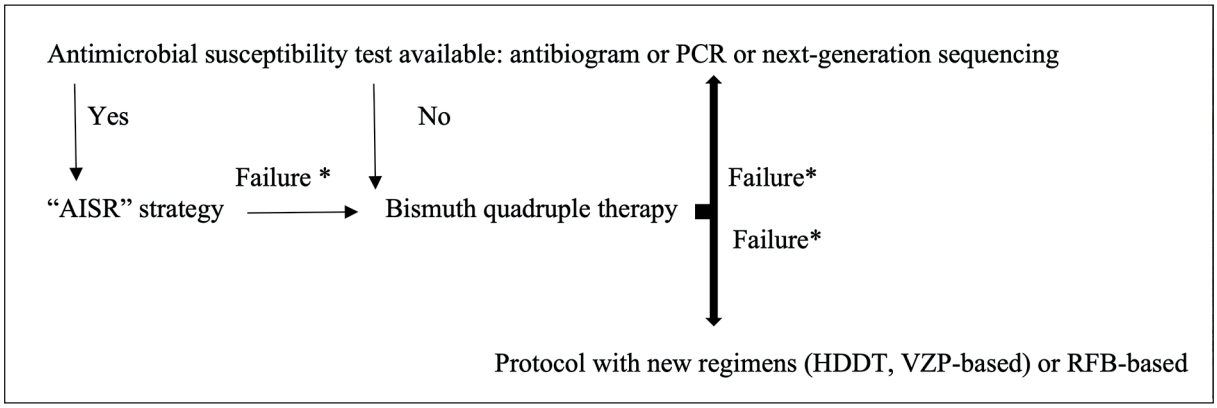

Figure 1. Helicobacter pylori-HIV co-infection: a strategy to eradicate *H. pylori* and to "save" gut microbiota. *It is mandatory to question patients' adherence before a subsequent-line treatment is prescribed.HIV: human immunodeficiency virus; "AISR": Antibiogram-interactions between drugs-supports (material, multimedia)-Referent physician; HDDT: High dose dual therapy; VZP: vonoprazan; RFB: rifabutin.

BISMUTH QUADRUPLE THERAPY

BQT is a powerful treatment that provides up to an 80% eradication rate as first-line empirical and rescue therapy in the general population[1,10,12-15]. BQT as a second- and third-line therapy for 14 days is associated with an eradication rate of 78 to 80%10. A meta-analysis of 38 studies looking at the use of BQT as rescue therapy after first-line failure with CLA-based triple therapy was performed. The cumulated eradication rate by ITT analysis was 78% (95%CI [75-81]) with 76%, 77%, and 82% for 7, 10, and 14-day treatment durations, respectively. In Korea, Lee et al[12] showed that the efficacy of BQT after second-and third-line treatment failure was 66.7% by ITT analysis.

BQT is effective also after numerous failures, allowing an eradication by ITT of 84%. The eradication rates were 91% (67/74), 71% (17/24), 92% (11/12), and 75% (6/8) after 2, 3, 4 and 5 failures, respectively. However, the eradication rate dropped from 90% to 55% for those who received this treatment before[14].

The use of an optimal dose of esomeprazole (ESO) (40 mg twice daily) is significantly more effective than a lower dose (20 mg twice daily) (p<0.005). Resistance to MTZ only slightly affects the efficacy of BQT compared to its efficacy in other regimens. The optimal dose of MTZ that is required in a bismuth-containing regimen is 1.5 to 2 g per day. In France, the BQT is recommended as the first-line treatment given the high rate of CLA resistance[10,15].

H. pylori primary resistance to single and multiple antibiotics seems more common in PLWH than in the general population, whose consequence is a failure of empirical treatments. Interestingly, in our previous study, a subgroup of 11 *H. pylori*-HIV co-infected individuals, showing multiple primary antibiotic resistance, received BQT for 10 days as first-line treatment, achieving an eradication rate of 100%[7,8].

Overall, BQT is the best option in the presence of increased and multiple antibiotic resistance, achieving a high level of eradication as both first line and rescue therapy in the general population and probably also in people with HIV infection (Figure 1). There is a need for more studies on the latter group. The use of ESO (40 mg twice a day) is suitable and also optimal. The duration of at least 10 days and maybe 14 days is optimal[1,11].

OTHER TREATMENT REGIMENS

High dose dual therapy

High dose dual therapy (HDDT) consists of combining a PPI and AMX at a frequency of three to four times a day. The advantage to the use of AMX is virtually the absence of resistance

in many regions as well as in our PLWH. The bactericidal effect of AMX is time-dependent, meaning that it increases with the frequency of administration. In addition, AMX is stable at neutral intragastric pH achieved by frequent PPI administration. A neutral pH also constitutes a suitable environment in which *H. pylori* can replicate. Hence, the conjunction of neutral gastric pH and a stable and frequent dose of AMX at the time of higher *H. pylori* replication provides a high eradication rate of susceptible bacteria.

Currently, HDDT is not widely prescribed, except in China and Turkey[10,16-19]. In China, a randomized trial compared two groups. One group of 450 patients naïve for *H. pylori* treatment received empirical treatment with HDDT (rabeprazole (RPZ) 20 mg, AMX 750 mg) for 14 days (n=150) *vs.* Sequential treatment (Seq) for 10 days (n=150) *vs.* standard triple therapy (S3T) for 7 days (n=150). The ITT eradication rate was 95.3% for HDDT, 85.3% for Seq, and 80.7% for S3T. Another experimental group of 168 patients requiring *H. pylori* treatment received HDDT (PPI and AMX tid) (n=56), Seq (n= 56), or S3T (n=56) as second-line treatment. The ITT eradication rate was 89%, 52%, and 79% for HDDT, Seq, and S3T, respectively[16].

In Turkey, a randomized trial compared HDDT (RPZ 20 mg + AMX 750 mg) (n=98) and BQT [sous-citrate bismuth 120 mg, four times daily + tetracycline (TCN) 500 mg, four times daily + MTZ 500 mg, tid + RPZ 20 mg twice daily] (n=98). The ITT eradication rate was quite similar for HDDT and BQT: 84.9% and 87.8%, respectively. There was significantly more nausea, abdominal pain, dysgeusia, diarrhea, and headaches in the BQT[17].

Another advantage of HDDT is the reduced number of pills, leading to a better tolerance, and the use of an antibiotic for which the resistance rate is very infrequent. However, the administration frequency of 3 to 4 times in a day is a weakness.

Given the rising rate of the primary resistance to multiple antibiotics and infrequent AMX resistance of *H. pylori* strains isolated in HIV co-infected people, a new regimen like HDDT is interesting (Figure 1). In our center, three PLWH who experienced >2 *H. pylori* eradication failures, one of which suffered from kidney insufficiency, were cured with HDDT. However, the efficacy of HDDT among *H. pylori*-HIV co-infected people needs further evaluation.

POTASSIUM-COMPETITIVE ACID BLOCKER-BASED THERAPY

Potassium-competitive acid blockers (P-CABs) are a novel class of potent agents that block H+-K+-ATPase on parietal cells in the stomach, producing a rapid and deep inhibition of acid secretion leading to a rise in intragastric pH. The P-CAB first-generation, vonoprazan (VPZ), is mainly available in East Asia where it has been prescribed as a VPZ-based dual and triple therapy against *H. pylori* infection. The VPZ-triple therapy (VPZ + two antibiotics) for 14 days is well-tolerated, achieving an *H. pylori* eradication rate of 95%. VPZ dual therapy (VPZ + one antibiotic) has shown an *H. pylori* eradication rate of 85%. Polymorphism of the hepatic isoenzyme CYP2C19 does not affect the treatment efficacy[20-22]. With such high efficacy, VPZ-based therapy could be also evaluated in *H. pylori*-HIV coinfected people (Figure 1).

RIFABUTIN-BASED THERAPY

Rifabutin (RFB) is an antibiotic used against *Mycobacterium tuberculosis,* the responsible agent for tuberculosis (TB). *H. pylori* resistance to RFB is very low in the range of 1-2%. The RFB-containing regimen consists of RFB + AMX + PPI. It achieved an eradication rate of 79%, 66% to 70%, and 52% after the second, third, and fourth line, respectively. The overall eradication rate as a rescue therapy is around 73%. Ten days is more effective than seven days of treatment. However, some factors limit its use, in particular, the possible induction of *M. tuberculosis* resistance to rifampicin (RIF), medullar toxicity, availability, and cost[10,23-25].

Taking into account the above considerations, RFB-containing treatment is not used as a first-line treatment but is reserved for treatment after multiple (>3) failures to eradicate *H. pylori* infection. Moreover, for its use in PLWH, it is necessary to rule out latent TB given the risk of RFB to induce *M. tuberculosis* resistance to RIF.

FAILURE OF FIRST-LINE THERAPY

H. pylori resistance to antibiotics has been widely studied in the general population, in contrast to PLWH. In three recent studies, we observed that single and multiple resistance were significantly higher in PLWH than in the controls[1,6-8,10]. Therefore, most empiric treatments can lead to a greater rate of failure, and subsequent cures will impair the microbiota diversity. Consequently, the use of AST (culture + antibiogram or PCR) provides the best chance to eradicate *H. pylori* in PLWH. If AST and BQT are not available, a treatment like HDDT in a study protocol is an option. VPZ-based therapy, currently available only in Asia, provides a high efficacy against *H. pylori*[1,6-8,10].

ADHERENCE ISSUE

PLWH always receives poly-medication against HIV and comorbidities that increase with aging. Therefore, issues related to poly-medication (number, frequency, duration, side effects, and drug interactions) require careful consideration. For instance, we found that ARVs and poly-medication could affect negatively the *H. pylori* eradication rate in co-infected individuals, compared to no ARV treatment. We believe that if there is a pill's burden, it is essential to assess a way to support (material, multimedia) the patient, notably upon initiation and throughout treatment. Consequently, a patient who observes the motivation of the staff for his well-being will be encouraged. When possible, the choice of a simple but potent *H. pylori* eradication regimen (few pills, less often, well-tolerated) can also be a help in improving the patient's adherence to the regimen. And excellent adherence can contribute to saving costs (financial, and microbiota)[8,26-28].

PRESERVATION OF MICROBIOTA

In a previous study, we showed that macrolide and quinolone consumption are more frequent in PLWH than in the general population. It is known that antibiotic consumption favors the development of resistant strains in the microbiota. Furthermore, HIV infection *per se* also alters the body's microbiota. Altogether, HIV infection causes immune dysfunction leading to more frequent infections; they then necessitate antibiotic treatment that further alters the gut microbiota, creating the source of the development of chronic disease. Since HIV infection is currently a chronic disease necessitating long-term ARV treatment, the microbiota of PLWH needs to be preserved. That could be achieved by adopting a potent antibiotic strategy that limits the number of attempts, e.g., for *H. pylori* infection eradication treatment, by using an AST-guided and powerful treatment, rending the adherence near-perfect[1,7,29,30].

CONCLUSIONS

We suggest that treatment of *H. pylori* infection among *H. pylori*-HIV co-infected patients be based on the AISR strategy while, in fact, currently BQT is probably the sole acceptable empirical treatment. If both regimens are not locally available, the *H. pylori* treatment to prescribe may be based on the local knowledge of ecology and of locally proven effective anti-*H. pylori* regimens. Dual therapy especially with VPZ is an interesting alternative to consider for a study protocol in an area where the prevalence of AMX resistance is low. *H. pylori* eradication strategies should try to preserve microbiota, in particular, in PLWH. More data and guidelines on the treatment of *H. pylori* in *H. pylori*-HIV co-infected people will be necessary for the future.

Conflict of Interest

The author declares no conflict of interest.

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