DOI: 10.1111/hiv.13083

HIV Medicine (2021), **22**, 547–556

ORIGINAL RESEARCH

Failure to eradicate *Helicobacter pylori* infection is more frequent among HIV-positive patients

M Nkuize[1] J Vanderpas,[2] M Buset,[1] M Delforge,[3] G-B Cadière[4] and S De Wit[3]

[1]*Department of Gastroenterology, University Hospital Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium,* [2]*Department of Hospital Hygiene, University Hospital Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium,* [3]*Department of Infectious Diseases, University Hospital Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium and* [4]*Department of Digestive Surgery, University Hospital Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium*

Objectives

Helicobacter pylori is a worldwide infection, but little is known about the efficacy of treatment for *H. pylori* infection in HIV-positive patients. The goal of this work was to evaluate outcomes after first-line *H. pylori* treatment and identify risk factors for failure in HIV-positive patients.

Methods

This registry study of unmatched *H. pylori*-infected HIV-positive patients and HIV-negative obese pre-bariatric surgery controls was performed in a tertiary university hospital. Cases were enrolled from 2006 to 2017, controls from 2007 to 2014, and both received standard of care. An additional 'optimal' subgroup of cases was enrolled prospectively from 2017 to 2019 which was treated only on the basis of antibiogram, drug interaction search and additional support by one referent physician. *Helicobacter pylori* eradication failure rates were compared according to clinical, microbiological and pathological parameters and treatment.

Results

We analysed 258 HIV-positive patients and 204 HIV-negative control patients. *Helicobacter pylori* eradication failure rates were markedly greater in cases (24.1%) than in controls (8.8%). The proportions of levofloxacin and metronidazole resistance were greater in cases than in controls ($P < 0.05$). Among cases treated with *H. pylori* triple therapy (S3T), the 'optimal' subgroup experienced a 9.5% failure rate *vs.* 28.6% with other strategies ($P = 0.01$). Risk factors for failure were *H. pylori* treatment strategy, exposure to antiretroviral treatment, and alcohol status. Overall, positive HIV status was a risk factor for S3T eradication failure.

Conclusions

Patients co-infected with *H. pylori* and HIV frequently failed to eradicate *H. pylori* and this was related to treatment strategy, antiretroviral exposure and lifestyle.

Keywords: co-infection, drug interactions, *Helicobacter pylori*, HIV, microbial susceptibility test, risk factors, treatment outcome

Accepted 18 January 2021

Introduction

Treatment of *Helicobacter pylori* infection prevents gastroduodenal complications [1–3]. Worldwide, among numerous regimens against *H. pylori* infection, the standard triple therapy (S3T), a combination of two antibiotics and a proton pump inhibitor (PPI), is widely used [1,2]. However, the failure rate for S3T has increased in recent years, ranging from 20% to 30% [4,5]. The main reasons for this are related to increased antibiotic resistance and poor treatment compliance (dosage, duration, frequency) [4–6]. Moreover, host genetic factors such as PPI metabolism and interleukin-1B (IL-1B) polymorphisms may be involved [7–9]. Graham *et al.* [10] have suggested that the standard of care should target a response rate of at least 90–95% with an accepted cure rate ≥ 80%.

These complications are also found in HIV-infected individuals who are co-infected with *H. pylori* [11–14]. However, evidence of the effectiveness of *H. pylori*

Correspondence: Marcel Nkuize, Department of Gastroenterology, University Hospital Saint Pierre, Université Libre de Bruxelles, 322, Rue Haute, Brussels 1000, Belgium. Tel: +32 5354200; fax: +32 5353686; e-mail: marcelnkuize@hotmail.com

infection treatment among HIV-infected patients is limited compared with the general population [1,3]. This longitudinal study of individuals co-infected with *H. pylori* and HIV has two objectives: (1) to describe the different regimens used and eradication rates of first-line therapies against *H. pylori* infection, and (2) to identify predictors of *H. pylori* treatment failure.

Methods

This longitudinal unmatched case–control registry-based study included outpatients from University Hospital Saint Pierre, Brussels (Belgium), a general tertiary hospital. Patients were scheduled for treatment after a positive diagnosis of *H. pylori* infection. They were divided into three groups: (1) cases were HIV-positive individuals enrolled from 1 January 2006 to 31 August 2017; (2) controls were obese individuals who were candidates for bariatric surgery enrolled from 1 January 2007 to 31 December 2014; and (3) an 'optimal' subgroup of HIV-positive individuals who received optimal *H. pylori* treatment defined as *H. pylori* treatment administered to individuals receiving HAART (highly active antiretroviral therapy), integrating exposure to HAART, antimicrobial susceptibility testing, a course of 14 days, and drug–drug interactions. A single specialist physician experienced in *H. pylori* therapy provided care as described in the following. Consecutive individuals were recruited prospectively from 10 October 2017 to 10 September 2019.

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the local hospital ethics committee of University Hospital Saint-Pierre, Brussels. All procedures described in the study were performed for routine medical purposes. Written consent from patients was obtained according to regulatory rules. The study was registered with ISRCTN registry number 16935348.

Inclusion criteria for cases and controls were as follows: age $\geq$ 18 years, *H. pylori* infection proven by either culture with antimicrobial susceptibility test (AST) or pathology examination of gastric samples obtained through upper gastrointestinal (GI) endoscopy, and no prior history of *H. pylori* treatment. Exclusion criteria were: pregnancy, partial or total gastrectomy, disagreement to participate, prior history of *H. pylori* treatment, history of anti-*H. pylori* antibiotic allergy, end-stage liver or kidney dysfunction.

Demographic data and clinical parameters, including pathological and microbiological results of positive biopsy samples, were collected. Parameters analysed included demographics [age ($<$ 50 and $\geq$ 50 years), gender, ethnicity (sub-Saharan and North Africans, European and other), body mass index (BMI, kg/m^2), alcohol or tobacco consumption (current drinker/smoker or not)]; HIV status, including Centers for Disease Control and Prevention (CDC) stage, immune profile [CD4 T lymphocytes (T CD4)], HIV viral load (at the time of anti-*H. pylori* treatment), HAART status (not treated, treated and class composition) and non-HAART co-medication use, including chemoprevention of opportunistic infections with macrolides, trimethoprim-sulfamethoxazole, and co-medication against dyslipidaemia, diabetes, arterial hypertension, cardiomyopathy, coagulation disorders, depression, anxiety, seizures, as well as painkillers, vitamin D supplementation and acetylsalicylic acid; *H. pylori* treatment (PPI and antibiotics, dose, frequency, duration, side effects, tolerability, compliance and strategy: empirical, AST-guided, optimal, and non-optimal); and treatment outcome evaluated by urea breath test (UBT).

Tolerability of S3T refers to 'the degree to which overt adverse effects can be tolerated by the subject': adverse effects (AEs) were collected 'on' treatment using an adapted questionnaire ['Have you experienced new complaints since you started treatment? If yes, specify and score severity as none or mild, moderate, severe, and very severe according to the effect on your daily life activities (not limited at all or a little bit) and whether AEs interfered with the treatment (somewhat or not interfering with the treatment, quite a bit and interfering with the treatment, and very much and treatment was discontinued with rapid resolution of symptoms afterward)'] [15].

Compliance was evaluated at the end of treatment by counting the pills left in the diaries and was considered to be 'good' if the patient took > 90% of the dose course at the full dose of the prescribed treatment > 90% of time [15].

Antimicrobial susceptibility tests were performed by disk diffusion and agar dilution methods (Neo-Sensitabs; Rosco, Taastrup, Denmark); and minimum inhibitory concentration was determined by agar dilution method. Isolates were classified as resistant with cut-off values of $\geq$ 1 mg/L for clarithromycin (CLA), > 8 mg/L for metronidazole (MTZ), and > 1 mg/L for levofloxacin (LEV) [16,17].

Immunohistological staining was used to diagnose *H. pylori* infection. All slides were interpreted by the same pathologist according to the updated Sydney scoring system [18].

Post-UBT, any upper GI endoscopy performed for whatever reason, such as control of gastric ulcer, included gastric biopsies for *H. pylori* diagnosis by pathology and microbiology examination. After bariatric

surgery, pathological examination of gastric explants included examination for *H. pylori* infection.

Depending on patient anamnesis and the availability or not of antibiotic susceptibility testing results, physicians subjectively decided to prescribe one of the following regimens [2,3]: (1) S3T: a PPI plus two antibiotics (amoxicillin (AMX), CLA or MTZ) twice daily for 7–14 days; (2) sequential therapy: a PPI plus AMX twice daily for 5 days followed by a PPI plus CLA and MTZ twice daily for 5 days; (3) quadruple therapy pharmacy preparation of capsules: including tetracycline (TET)-chlorhydrate 500 mg plus colloidal bismuth subcitrate 500 mg four times daily, MTZ three times daily, and PPI twice daily for 10 days [19]; (4) another quadruple therapy, single pill formulation, containing bismuth subcitrate 140 mg/TET-chlorhydrate125 mg/MTZ 125 mg (three pills to take four times daily) plus one PPI (two times daily) for 10 days [20]; or (5) concomitant therapy : PPI plus three antibiotics (AMX, CLA, MTZ) twice daily for 14 days. PPIs used were esomeprazole 40 mg (mainly used in 'optimal' strategy), lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg or rabeprazole 20 mg. Antibiotic doses were AMX 1000 mg, CLA 500 mg, MTZ 500 mg.

Helicobacter pylori treatment strategy was defined as based or not on antibiotic susceptibility testing as empirical (individuals treated on the basis of positive pathology examination alone, without AST), AST-guided (AST was available but not always completely adhered to when making decisions on treatment), or optimal therapy for *H. pylori* in HIV-infected individuals as described earlier and, in addition, a single physician experienced in *H. pylori* therapy provided care as follows: (1) patient received oral explanation of treatment and associated side effects, and simple support material (Appendix S1) indicating drugs and drinking instructions (if necessary, in the patient's language); (2) at day 2 (or 3) 'on' treatment, the nurse or physician had phone contact with the patient for coaching and to ask about any side effects, and a visit to the clinic was planned if the patient experienced any problems related to the prescribed medications; (3) patients were seen by the medical staff once the treatment ended in order to get further information (tolerability, compliance) and to plan the UBT.

Helicobacter pylori eradication was defined as no detection of *H. pylori*: at UBT performed in all patients, as described previously [21], $\geq$ 6 weeks after treatment completion [3], or in other examinations (e.g. pathology examination of gastric biopsies from upper GI endoscopy performed after healing of *H. pylori* to monitor gastric lesions or gastric explants of HIV-negative obese patients undergoing bariatric surgery); and at control UBT performed 6 months after an early inconclusive test.

All authors had access to the study data and reviewed and approved the final manuscript.

Statistical analysis

According to the unmatched case–control study design, the threshold of statistical significance was defined by the Breslow & Day method using EpiInfo™ software [22,23]. For a cohort of 484 individuals, including 242 cases and 242 controls, and an 8% *H. pylori* eradication failure level in the control group, the percentage of exposure in the case group had to be > 17% to obtain a significant difference at the alpha-level of 0.05 with 80% power.

Univariable analysis was used to compare the distribution of variables: HIV-positive *vs.* HIV-negative individuals; and among HIV-positive individuals, those not-treated *vs.* those treated with HAART. For the comparison of continuous variables normally distributed or not, Student's *t*-test or the Mann–Whitney test was used. For the comparison of two or more categorical variables, Fisher's exact test or the Pearson χ^2 test was used. Adjustments of categorical variables for confounding variables, and odds ratios (OR) with 95% confidence intervals (95% CsI) were measured with the Mantel–Haenszel method. All statistical significance measurements were two-tailed. There was no correction for multiple comparisons.

Variables with a statistical significance ≤ 0.1 in univariable analysis were included in a binary logistic regression. Baseline variables in the univariable analysis of cases and controls were as follows: age, gender, ethnicity (black African *vs.* others), HIV serology/RNA, tobacco habits and alcohol intake, *H. pylori* treatment [type, duration, treatment year and strategy (such as Optimal versus non-optimal)], co-medication and AST results. Baseline variables in the univariable analysis of cases were age, gender, ethnicity, tobacco habit, alcohol intake, CD4 T cell count, HAART, non-HAART co-medication and S3T therapy against *H. pylori* [duration, year of treatment and strategy (such as optimal *vs.* other)]. For statistical purposes, the variable '*H. pylori* treatment' was defined as two strategies, 'optimal' and 'other', which combined the 'empirical' and AST-guided strategies. This was in order to determine the outcome of the new 'optimal' strategy *vs.* others (non-optimal) as each of the components was studied separately in the whole cohort.

Any patient who received at least one dose of treatment was included in the statistical analysis. The IBM SPSS Statistics v.25 - 08/2018 (IBM Corporation, New York, NY, USA) was used for the statistical analysis. Significance was assumed at a $P < 0.05$ threshold.

Results

A total of 462 consecutive patients (Fig. 1) were included: 258 HIV-positive cases and 204 HIV-negative controls. Table 1 summarizes the demographic data. Both groups were similar with regard to the proportion of patients aged < 50 *vs.* ≥ 50 years, but dissimilar for ethnic distribution, sex ratio, smoking habits, alcohol intake and non-HAART co-medication.

Helicobacter pylori antimicrobial susceptibility testing to AMX, CLA, LEV, MTZ and TET was available for 135 cases and 106 controls. Distribution of resistance to antibiotics

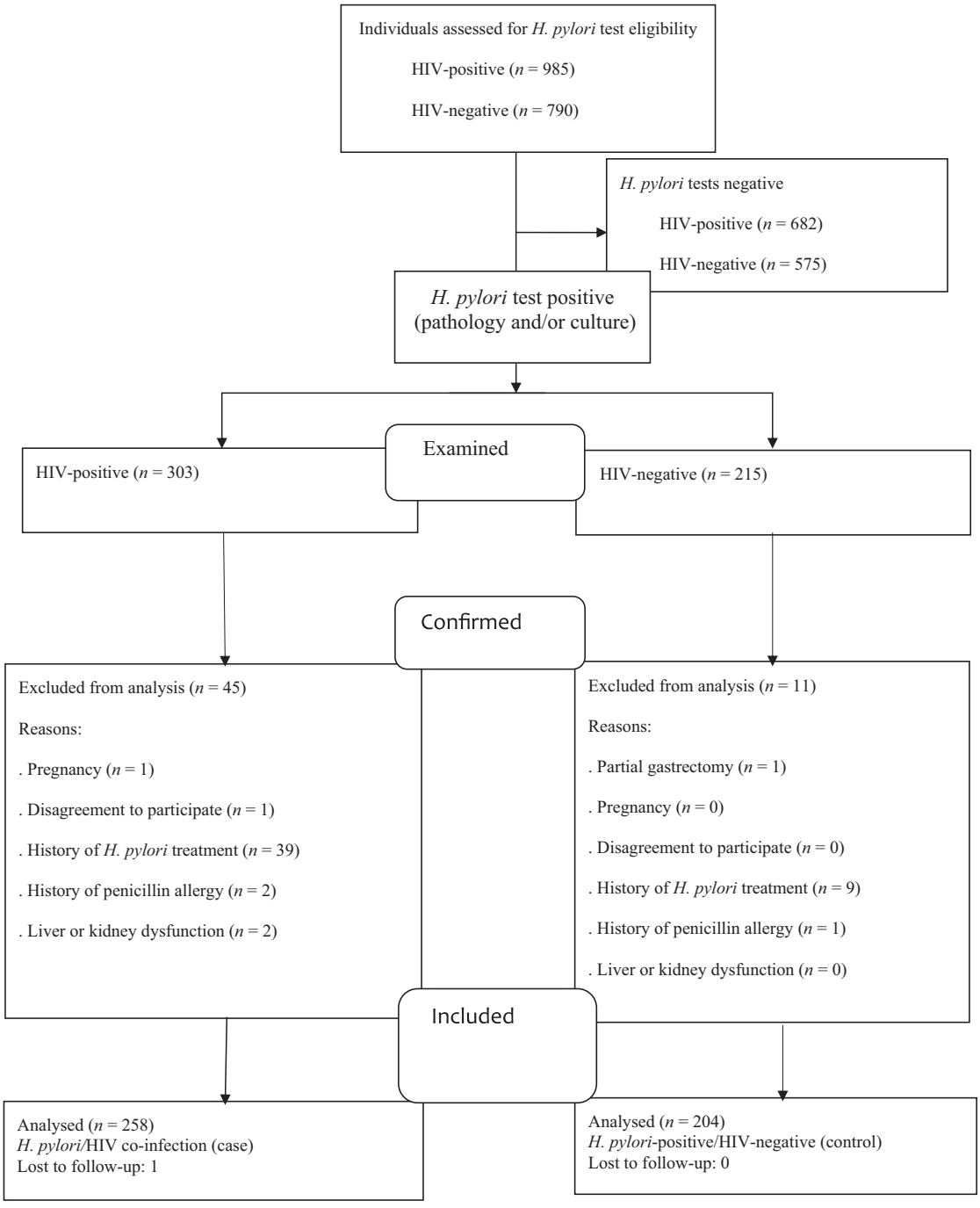

Fig 1 Flow diagram

Table 1 Baseline characteristics of cases and controls

Characteristics	HIV-positive (n = 258)	HIV-negative (n = 204)	P-value
Demographics			
Age (years) [mean ± SD (*N*)]	43.4 ± 10.9 (258)	39.1 + 12.1 (204)	< 0.0001
Age < 50 years [*n*/*N* (%)]	195/258 (75.6%)	161/204 (78.9%)	0.4
Male gender [*n*/*N* (%)]	127/258 (49.2%)	56/204 (27.5%)	< 0.0001
Body mass index (kg/m^2) [mean ± SD (*N*)]	26.2 ± 6.3 (237)	42.2 ± 5.7 (204)	< 0.0001
Ethnicity			
Sub-Saharan African [*n*/*N* (%)]	160/258 (62.0%)	35/198 (17.7%)	< 0.0001
North African [*n*/*N* (%)]	11/258 (4.3%)	46/198 (23.2%)	
European [*n*/*N* (%)]	70/258 (27.1%)	115/198 (58.1%)	
Other [*n*/*N* (%)]	17/258 (6.6%)	2/198 (1.0%)	
Lifestyle			
Tobacco smokers [*n*/*N* (%)]	70/252 (27.8%)	31/203 (15.3%)	0.001
Alcohol drinkers [*n*/*N* (%)]	90/251 (35.9%)	24/203 (11.8%)	< 0.0001
Co-medication non-HAART			
≥ 2 non-HAART co-medications [*n*/*N* (%)]	67/258 (26.0%)	28/187 (15.0%)	0.006
Microbiology*			
No antibiotic resistance [*n*/*N* (%)]	38/135 (28.1%)	56/104 (53.8%)	0.0001
Resistance to one antibiotic [*n*/*N* (%)]	57/135 (42.2%)	35/104 (33.7%)	
Resistance to two antibiotics [*n*/*N* (%)]	36/135 (26.7%)	13/104 (12.5%)	
Resistance to three antibiotics [*n*/*N* (%)]	4/135 (3.0%)	0/104 (0.0%)	
Resistance to:			
Clarithromycin [*n*/*N* (%)]	23/135 (17.0%)	11/106 (10.4%)	0.1
Levofloxacin [*n*/*N* (%)]	47/135 (34.8%)	14/106 (13.2%)	0.0001
Metronidazole [*n*/*N* (%)]	71/135 (52.6%)	38/106 (36.5%)†	0.01
HAART-treated** [*n*/*N* (%)]	201/258 (77.9%)	–	NA
CD4 T lymphocytes (cells/μL) [median (IQR) (*N*)]	527 (360–729) (258)	–	NA
HIV viral load (copies/mL) [median (IQR) (*N*)]	50 (20–531) (257)	–	NA

n, no. meeting the characteristic; *N*, total no. of observations.
†2 strains death.
*Of 241 individuals, the distribution of resistance to antibiotics were 34/241 (14.1%) for clarithromycin, 61/241 (25.3%) for levofloxacin, and 109/239 (45.6%) for metronidazole.
**See Supplementary Appendix S2 for more details.

was 34/241 (14.1%) for CLA, 61/241 (25.3%) for LEV and 109/239 (45.6%) for MET. No AMX or TET resistance was observed. The proportion of patients who harboured strains with resistance to at least one of CLA, LEV or MTZ and the proportion with resistance to MTZ and LEV were significantly greater in cases than in controls. The proportion with CLA resistance was greater in cases than in controls, but the difference was not statistically significant.

At the time of *H. pylori* treatment of cases, median [interquartile range (IQR)] CD4 T-cell count was 527 cells/μL (360–729) and median (IQR) viral load was 50 copies/mL (20–531). In all, 201 cases (77.9%) were on HAART, the composition of which is presented in Appendix S2. In the optimal subgroup, HAART was switched to avoid drug–drug interactions in 9/42 (21.4%) cases.

Table 2 summarizes *H. pylori* treatment received: S3T in 401 patients (most prescribed in both groups), sequential in 48 (more prescribed in controls), bismuth quadruple therapy (BQT) in 11 and concomitant therapy in two (both only in cases).

Among the 401 individuals treated with S3T, the strategy for antibiotic administration in relation to antibiotic susceptibility test was: 'empirical' for 191 individuals (46.2% of cases and 49.4% in controls), AST-guided for 167 individuals (38.4% in cases vs 50.6% in controls), and optimal for 43 cases.

A 7-day course of treatment was more common in cases than in controls: 122 of 258 (47.3%) *vs.* 35 of 204 (17.2%), respectively.

Table 3 summarizes *H. pylori* treatment outcome failures in cases and controls. With regard to treatment classes, failure was significantly more common in cases (25.0%) than in controls (9.1%) for S3T; the difference in treatment failure was of the same order of magnitude for sequential treatment (cases, 20%; and controls, 7.1%), even if not statistically significant.

When looking at S3T class as a function of treatment strategy, failure rates were significantly greater in cases for both AST-guided and empirical strategies. Remarkably, the optimal strategy demonstrated a level of *H. pylori* eradication failure rate similar to that observed in controls. Adverse events were mild to moderate in 87% and 93% of cases and controls, respectively. Severe adverse events were reported and lead to treatment dose

Table 2 Characteristics of *Helicobacter pylori* treatment in cases and controls

Characteristics	HIV-positive	HIV-negative	*P*-value	
	[*n*/*N* (%)]	[*n*/*N* (%)]		
Anti-*H. pylori* treatment				
S3T	225/258 (87.2%)	176/204 (86.3%)		
Empirical	104/225 (46.2%)	87/176 (49.4%)		
AST-guided	78/225 (34.7%)	89/176 (50.6%)	< 0.0001	
Optimal	43/225 (19.1%)*	0/176 (0.0%)		0.002
Sequential	20/258 (7.8%)	28/204 (13.7%)		
Bismuth quadruple therapy	11/258 (4.3%)	0/204 (0.0%)		
Concomitant	2/258 (0.8%)	0/204 (0.0%)		
Duration of S3T				
7 days	122/258 (47.3%)	35/204 (17.2%)	< 0.0001.	
10 days	83/258 (32.2%)	169/204 (82.8%)		
14 days	53/258 (20.5%)	0.0 (0.0%)		
Calendar period of treatment				
2003–2006	39/258 (15.1%)	0/204 (0.0%)	< 0.0001	
2007–2014	143/258 (58.1%)	204/204 (100.0%)		
2015–2019	46/258 (26.7%)	0/204 (0.0%)		

AST, antimicrobial susceptibility test; *n*, no. meeting the characteristic; *N*, total no. of observations; S3T, standard triple therapy.
*One lost to follow-up after inclusion.

Table 3 *Helicobacter pylori* treatment failure in cases and controls

Characteristics	HIV-positive [*n*/*N* (%)]	HIV-negative [*n*/*N* (%)]	*P*-value
Class of treatment			
S3T	56/224 (25.0%)	16/176 (9.1%)	< 0.0001
Sequential	5/20 (20.0%)	2/28 (7.1%)	0.111
Bismuth quadruple therapy	0/11 (0.0%)	–	NA
Concomitant	1/2 (50.0%)	–	NA
Overall	62/257 (24.1%)	18/204 (8.8%)	< 0.0001
S3T*			
Empiric	25/104 (24.0%)	7/87 (8.0%)	0.003
AST-guided	27/78 (34.6%)	9/89 (10.1%)	0.0001
Optimal	4/42 (9.5%)†	–	NA
Overall	56/224 (25.0%)	16/176 (9.1%)	< 0.0001

AST, antimicrobial susceptibility test; *n*, no. meeting the characteristic; *N*, total no. of observations; NA, not applicable; S3T, standard triple therapy; optimal, optimal therapy of *H. pylori* in HIV-positive individuals.
*Among ST3 patients, side effects were none or mild in 196/225 (87.1%) cases and 164/176 (93.1%) controls, moderate in 27/225 (12.0%) cases and 11/176 (6.2%) controls, severe leading to treatment dose reduction in 12/225 (5.3%) cases and 2/176 (1.1%) controls, and severe leading to treatment discontinuation in two (0.8%) cases. The two cases with severe side effects were allergic reactions with diffuse rash and dizziness. There were no cases of life-threatening conditions. 'Good' compliance to treatment was achieved in 211/225 (93.7%) cases and in 174/176 (98.8%) controls.
†Three out of four failures were due to proton pump inhibitor and antibiotic dose reduction.

reduction in 12/225 (5.3%) cases and 2/176 (1.1%) controls and to treatment discontinuation in two (0.8%) cases.

Risk factors of *H. pylori* treatment failure in 461 individuals were evaluated by univariable analysis. Six baseline characteristics were significantly associated with greater proportions of *H. pylori* eradication failure [age ≥ 50 years; alcohol drinker; tobacco smoker; HIV-positive status; duration of *H. pylori* therapy (7 days)] with a *P*-value ≤ 0.1 (Table 4). The other baseline characteristics did not reach statistical significance and were not included in the multivariable analysis. In the multivariable analysis, only HIV-positive status remained significantly associated with increased risk of *H. pylori* eradication failure ($P < 0.05$). When restricting the analysis to S3T *H. pylori* treatment subcohort (Appendix S3), the results were similar.

Analysis of risk factors of *H. pylori* treatment failure in cases was restricted to subjects treated with S3T, to include HIV-related variables (CD4 count, HAART treatment, CDC stage) (Table 5). Univariable analysis showed a favourable association ($P \leq 0.1$) of alcohol abstinence, no HAART treatment, non-HAART co-medication, CD4 count < 500 cells/μL, CDC stage 2 or 3 at *H. pylori* treatment, and optimal with eradication of *H. pylori*. When introducing these factors in multivariable analysis by logistic regression, alcohol abstinence, non-HAART treatment, and optimal treatment reached a significance level of $P < 0.05$.

Among cases treated with S3T *H. pylori* treatment, the optimal strategy achieved more successful eradication, with fewer failures than the AST-guided strategy [4/42 (9.52%) *vs.* 27/78 (34.6%); $P = 0.002$; OR (95% CI): 0.18 (0.06–0.616)], the empirical strategy [4/42 (9.5%) *vs.* 25/104 (24.04%); $P = 0.06$; OR (95% CI): 0.33 (0.1–1.0237)], and the non-optimal subgroup [(4/42 (9.5%) *vs.* 52/182 (28.5%); $P = 0.01$; 0.26 (0.089–0.774)].

The failure of S3T to eradicate *H. pylori*, stratified by CD4 T-cell count and HAART use, among 224 cases is presented in Appendix S4. Higher CD4 T-cell count

Table 4 Analysis of strength of association between *Helicobacter pylori* eradication failure and demographic variables, *H. pylori* therapy characteristics, and HIV status

Univariable analysis by Mantel–Haenszel method.*		Eradication failure [*n*/*N* (%)]			
Variable	**Category as group† 0 *vs.* 1**	**Group 0**	**Group 1**	**Unadjusted OR (95% CI)**	**Fisher's exact test**
Age	< 50 *vs.* ≥ 50 years	57/355 (16.1%)	23/106 (21.7%)	0.690 (0.402–1.187)	**0.1**
Gender	Male *vs.* female	34/183 (18.6%)	46/278 (16.5%)	1.151 (0.706–1.876)	0.6
Alcohol	Abstainer *vs.* drinker	46/340 (13.5%)	30/113 (26.5%)	0.433 (0.257–0.728)	**0.002**
Tobacco	Non-smoker *vs.* smoker	54/354 (15.3%)	23/100 (23.0%)	0.603 (0.348–1.043)	**0.07**
Ethnicity	Sub-Saharan *vs.* other	37/194 (19.1%)	43/261 (16.5%)	1.195 (0.736–1.941)	0.5
HIV	HIV-negative *vs.* HIV-positive	18/204 (8.8%)	62/257 (24.1%)	0.304 (0.174–0.534)	**< 0.0001**
Duration of *H. pylori* therapy	7 *vs.* 10–14 days	38/157 (24.2%)	42/304 (13.8%)	1.992 (1.221–3.250)	**0.006**
Type of *H. pylori* treatment	ST3 *vs.* other (seq., BQT, CoT)	72/400 (18.0%)	8/61 (13.1%)	1.454 (0.663–3.191)	0.4
Strategy of *H. pylori* therapy	Optimal *vs.* other	4/42 (9.5%)	76/419 (18.1%)	0.475 (0.165–1.371)	0.2
Year of *H. pylori* therapy	2003–2010 *vs.* 2011–2019	34/219 (15.5%)	46/242 (19.0%)	0.783 (0.481–1.274)	0.3
Non-HAART co-medication	0-1 *vs.* ≥ 2 non-HAART	53/349 (15.2%)	24/95 (25.3%)	0.530 (0.306–0.916)	**0.02**
Multivariable analysis by binary logistic regression (*N* = 415)			**Adjusted OR (95% CI)**	**Sign. LR**	
Age	< 50 yrs *vs.* ≥ 50 yr		0.951 (0.506–1.789)	0.8	
Alcohol	Abstainer *vs.* drinker		0.570 (0.321–1.011)	0.05	
Tobacco	Non-smoker *vs.* smoker		0.760 (0.418–1.383)	0.3	
HIV	HIV-negative *vs.* HIV-positive		0.419 (0.218–0.805)	**0.009**	
Duration *H. pylori* therapy	7 days *vs.* 10-14 days		1.561 (0.907–2.686)	0.1	
Non-HAART co-medication	0–1 *vs.* ≥ 2 *vs.* non-HAART		0.712 (0.385–1.316)	0.2	

BQT, bismuth quadruple therapy; CI, confidence interval; CoT, concomitant therapy; HAART, highly active antiretroviral therapy; *n*, no. meeting the characteristic; *N*, total no. of observations; OR, odds ratio; seq., sequential therapy; sign. LR, significant logistic regression.
**H. pylori* antibiotic resistance was not introduced because it decreased the number of observations from 461 to 239.
†Group 0 includes: age < 50 years, male, abstainer, Sub-Saharan, HIV-negative, 7 days, standard triple are two parameters, optimal, 2003-2010, and 0–1 non-HAART co-medication. Group 1 is the opposite of group 0 categories.

Table 5 Analysis restricted to 224 HIV-positive subjects treated using standard triple therapy (S3T) *Helicobacter pylori* treatment: strength of association of demographic variables, *H. pylori* treatment variables and HIV variables with *H. pylori* eradication failure proportion by univariable analysis (a) and multivariable analysis (b)

(a) Univariate analysis by Mantel–Haenzel method		Eradication failure [*n*/*N* (%)]			
Variable	**Category as group* 0 *vs.* 1**	**Group 0**	**Group 1**	**Unadjusted OR (95% CI)**	**Fisher's exact test**
Age	<50 yr *vs.* ≥50 yr	41/174 (23.6%)	15/50 (30.0%)	0.719 (0.358–1.447)	0.3
Gender	male *vs.* female	29/107 (27.1%)	27/117 (23.1%)	1.239 (0.676–2.271)	0.5
Ethnicity	Sub-Saharan *vs.* other	31/136 (22.8%)	25/88 (28.4%)	0.744 (0.403–1.373)	0.3
Alcohol	abstainer *vs.* drinker	28/142 (19.7%)	25/77 (32.5%)	0.511 (0.272–0.960)	**0.04**
Tobacco	not smoker *vs.* smoker	37/157 (23.6%)	16/62 (25.8%)	0.886 (0.450–1.746)	0.7
H. pylori antibiotic resistance	No resistance *vs.* resistance to ≥ one antibiotic	8/35 (22.9%)	23/85 (27.1%)	0.799 (0.317–2.010)	0.8
Strategy of *H. pylori* treatment	Optimal *vs.* other	4/42 (9.5%)	52/182 (28.6%)	0.263 (0.089–0.774)	**0.01**
HAART treatment	No-HAART *vs.* HAART	6/53 (11.3%)	50/171 (29.2%)	0.309 (0.124–0.769)	**0.01**
Non-HAART co-medication	0–1 *vs.* ≥ 2 non-HAART co-medications	34/161 (21.1%)	22/63 (34.9%)	0.499 (0.263–0.948)	**0.04**
Year of *H. pylori* therapy	2003–2010 *vs.* 2011–2017	29/110 (26.4%)	27/114 (23.7%)	1.154 (0.630–2.113)	0.6
CD4 T-cell count	≥ 500 *vs.* < 500 cells/μL	38/123 (30.9%)	18/101 (17.8%)	2.061 (1.090–3.898)	**0.03**
CDC stage at *H. pylori* treatment	1 *vs.* 2 or 3	43/155 (27.7%)	13/69 (18.8%)	1.654 (0.823–3.325)	**0.1**

(b) Multivariable analysis by binary logistic regression (*N* = 198)	Category as group* 0 *vs.* 1	Adjusted OR (95% CI)	Sign. LR
Alcohol	Abstainer *vs.* drinker	0.387 (0.19–0.837)	0.008
HAART treatment	No HAART vs HAART	0.219 (0.082–0.580)	0.002
Non-HAART co-medication	0–1 *vs.* ≥ 2 non-HAART co-medications	0.469 (0.218–1.005)	0.05
CD4 T-cell count	≥ 500 *vs.* < 500 cells/μL	1.683 (0.810–3.498)	0.1
CDC at treatment	1 *vs.* 2 or 3	2.112 (0.937–4.761)	0.07
Strategy of *H. pylori* treatment	Optimal *vs.* other	0.140 (0.044–0.446)	0.001

CI, confidence interval; HAART, highly active antiretroviral therapy; *n*, no. meeting the characteristic; *N*, total no. of observations; OR, odds ratio; sign. LR, significant logistic regression.
*Group 0: age < 50, male, Sub-Saharan, abstainer, no antibiotic resistance, no HAAART, non-HAART co-medication 0–1 drugs, period 2003–2010, CD4 ≥ 500 cells/μL, and CDC stage 1 at *H. pylori* treatment. Group 1 is the opposite of group 0 categories.

appeared to be associated with greater S3T *H. pylori* eradication failure.

The impact of viral load on *H. pylori* relapse rate varied by exposure or not to HAART and *H. pylori* treatment strategy. Also, time of exposure to HAART did not play a role in *H. pylori* eradication failure (data not shown).

Discussion

Our objective was to evaluate the real-life effectiveness of *H. pylori* infection treatment among HIV-positive individuals. We chose to compare HIV-positive patients (cases) and HIV-negative obese individuals (controls) because of sampling convenience. Both groups represent highly motivated subjects: cases are well informed and are made aware of the connection between compliance to antiretroviral therapy and favourable outcome in terms of viral replication and immune function, while controls who are candidates for bariatric surgery are highly motivated to comply with tests and treatments, particularly identification and eradication of *H. pylori* infection, which is one of the major criteria for surgery qualification. S3T was the most frequently prescribed regimen against *H. pylori* in both groups, although regimens against *H. pylori* were more diverse among cases. This diversity may simply reflect calendar recruitment periods and guideline changes [1,3].

Our main finding is that HIV status appears to be a powerful independent factor that impacts *H. pylori* treatment outcome, with a significantly greater rate of *H. pylori* treatment failure (24.1% *vs.* 8.8%), which is unacceptably high [10]. We have not identified any other studies in HIV-positive individuals that allow a comparison with our findings, suggesting that *H. pylori* infection treatment in HIV patients has raised little attention so far. This low effectiveness of *H. pylori* eradication in individuals co-infected with *H. pylori* and HIV is similar to that found in regions with a high prevalence of *H. pylori* primary antibiotic resistance [10].

Three independent risk factors for *H. pylori* S3T eradication failure were identified in our cases: antimicrobial susceptibility, HAART exposure and alcohol intake.

Antimicrobial susceptibility testing should be used to tailor *H. pylori* infection treatment in any *H. pylori*/HIV co-infected individual as these patients have a greater proportion of single and multiple antibiotic resistances [21]. The reason for more *H. pylori* antibiotic resistance may involve frequent antibiotic consumption [21] and other mecanism. *Helicobacter pylori* primary antibiotic resistance in HIV patients has been poorly documented [21] and *H. pylori*/HIV co-infected individuals have often been treated on the basis of recommendations for the general population, namely empirical treatment [3]. In our experience, empirical therapy was associated with a 2.85-fold greater *H. pylori* eradication failure. On the other hand, treating *H. pylori* infection among *H. pylori*/HIV co-infected individuals using the optimal strategy (based on AST, rule out drug interactions, with support material and phone calls on treatment, and a physician focused into *H. pylori* infection – acronym 'AISR') is protective, with only a 0.14 vs 2.85 *H. pylori* eradication failure. Another advantage of tailoring *H. pylori* treatment to AST is that it allows elective prescription of BQT for *H. pylori* strains with multiple antibiotic resistances, as we observed [1,3]. This strategy may avoid therapeutic escalation, which can increase the risk of antibiotic resistance and gut microbiota alteration.

Being on HAART was also an independent risk factor for failure to eradicate *H. pylori*. Head-to-head comparisons of *H. pylori*/HIV co-infected individuals, with or without HAART at the time of *H. pylori* treatment (Appendix S4), showed that those not receiving HAART had good outcomes, similar to controls. This observation should be interpreted cautiously; however,. 'old' HAART regimens administered as several pills with poor tolerability could impact patient compliance, impairing compliance with *H. pylori* treatment [24]. Drug–drug interactions may also play a role, as *H. pylori* eradication failure tended to be more common among individuals treated with PI-containing regimens [25–27]. Recent HAART regimens are more simplified and fewer of them contain PIs. Issues related to HAART can be somewhat overcome as described in the optimal or AISR strategy: switching of HAART regimen in the case of drug interactions, allowing the use of potent and optimal doses of PPIs (such as esomeprazole 40 mg) that maintain gastric alkalinization for a longer period, enhancing the synergistic effect between S3T components and potentiating *H. pylori* eradication [3,8].

Alcohol intake is another factor that affects the outcome of *H. pylori* S3T. As a CYP3A4/5 or 2 C19 inducer and gastric emptying inhibitor, alcohol may reduce the efficacy of PPIs and antibiotics [9,28,29], while inducing disulfiram-like effects with *H. pylori* treatments containing MTZ, leading to altered compliance [30].

Despite ethnic differences in prevalence and drug metabolism, *H. pylori* eradication failure rates were similar in cases and controls among those of various ethnic origins [8,9,31].

Our study has limitations and strengths. It was a longitudinal observational survey based on a real-life clinical

registry. This approach is, by definition, limited to describing the strength of the associations between *H. pylori* outcomes and independent variables, without allowing for firm conclusions with regard to causal associations, which would require a randomized clinical study [8]. The use of an unmatched population and the inclusion of participants from different periods were also limitations. Potential confounding factors, such as CYP2C19 polymorphisms, were not studied in our routine practice. Direct measure of *H. pylori* inoculums from gastric samples by PCR (which is not routinely in use) rather than indirect measures by subculture (routine practice) from positive gastric biopsy cultures could provide, in addition to susceptibility, accurate quantification data as well as strain subtypes and could be used to tailor treatment duration according to certain threshold of inocula [31]. As for the strengths of this study, this is the first large case–control study involving consecutive HIV-positive individuals treated for *H. pylori* infection in different scenarios. It provides new and original data as most available data on *H. pylori* infection treatment are derived from the general population [3]. Similar evaluation methods were applied to all patients and these patients probably reflect those found elsewhere in similar conditions. Our results also identify specificities with regard to treating *H. pylori* infection in HIV-positive individuals, such as antimicrobial resistance, co-medications and drug interactions, and suggest how to improve the rate of successful eradication of *H. pylori* infection in that population.

In conclusion, our study highlights the fact that individuals co-infected with *H. pylori* and HIV have a high risk of first-line *H. pylori* eradication failure, which may be related to different factors such as antibiotic resistance, HAART exposure, drug interactions and lifestyle. Treatment of *H. pylori* infection in *H. pylori*/HIV co-infected individuals should be individualized as shown in the optimal strategy (AISR), which provided excellent outcomes.

In the future, direct bacterial quantification from gastric samples and CYP and IL-1B genotyping could be added to the treatment strategy in patients at risk of failure [8]. The treatment of *H. pylori* infection in HIV-positive individuals requires further studies and consideration at future consensus conferences on *H. pylori* infection.

Acknowledgments

We acknowledge the nurses of our endoscopy unit and our gastroenterologist colleagues, as well as Dr P. Itoudi who helped us throughout the study. We also thank the nuclear medicine and microbiology departments who performed UBT and antibiotic susceptibility testing, respectively, and FRPD ASBL (non-profit organization) for providing a portion of the material support. Help with English language editing and manuscript formatting were provided by Sandy Field, PhD, of Field Scientific LLC, who was compensated by the CHU St Pierre Department of Hepato-gastroenterology.

Conflict of interest: The authors have no conflicts of interest to declare.

Author contributions

MN contributed to the literature search, figures, study design, data collection, data analysis, data interpretation and manuscript writing. JV contributed to the literature search, figures, data analysis, data interpretation and manuscript writing. MB contributed to the study design, data interpretation and manuscript review. MD contributed to data collection, data analysis and manuscript review. G-BC contributed to data collection, data interpretation and manuscript review. SDW contributed to study design, data analysis, data interpretation and writing.

Data availability statement

The data underpinning this article will be shared by the corresponding author (MN) upon reasonable request.

References

1 Malfertheiner P, Megraud F, O'Morain CA *et al*. Management of *Helicobacter pylori* infection: the Maastricht IV/ Florence Consensus Report. *Gut* 2012;**61**:646e664.
2 Crowe SE. *Helicobacter pylori* infection. *N Engl J Med* 2019; **380**: 1158–1165.
3 Malfertheiner P, Megraud F, O'Morain CA *et al*. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6–30.
4 Gisbert JP, Pajares JM. *Helicobacter pylori* "rescue" regimen when proton pump inhibitor-based triple therapy fail. *Aliment Pharmacol Ther* 2002; **16**: 1047–1057.
5 Vakil N, Megraud F. Eradication therapy for *Helicobacter pylori*. *Gastroenterology* 2007; **133**: 985–1001.
6 Shiotani A, Lu H, Pina Dore M *et al*. Treating *Helicobacter pylori* effectively while minimizing misuse of antibiotics. *Cleve Clin J Med* 2017; **84**: 310–318.
7 Fischbach LA, Goodman KJ, Feldman M *et al*. Sources of variation of *Helicobacter pylori* treatment success in adults worldwide: a meta-analysis. *Int J Epidemiol* 2002; **31**: 128–139.

8 Uotani T, Miftahussurur M, Yamaoka Y. Effect of bacterial and host factors on *Helicobacter pylori* eradication therapy. *Expert Opin Ther Targets* 2015; **19**: 1637–1650.
9 Furuta T, Shirai N, Takashima M *et al.* Effect of genotypic differences in CYP2C19 on cure rates for *Helicobacter pylori* infection by triple therapy with proton pump inhibitor, amoxicillin, and clarithromycin. *Clin Pharmacol Ther* 2001; **69**: 158–168.
10 Graham DY, Hong L, Yoshio Y. A report card to grade *Helicobacter pylori* therapy. *Helicobacter* 2007; **12**: 275–278.
11 Nishimura S, Nagata N, Shimbo T *et al.* Factors associated with esophageal candidiasis and its endoscopy severity in the era of antiretroviral therapy. *PLoS One* 2013; **8**: e58217.
12 Nkuize M, De Wit S, Muls V *et al.* Upper gastrointestinal endoscopic findings in the era of highly active antiretroviral therapy. *HIV Med* 2010; **11**: 412–417.
13 Nevin TD, Morgan CJ, Graham DY *et al. Helicobacter pylori* gastritis in HIV-infected patients: a review. *Helicobacter* 2014; **19**: 323–329.
14 Ali Mohamed FA, Lule GN, Nyong'o A *et al.* Prevalence of *Helicobacter pylori* and endoscopic findings in HIV seropositive patients with upper gastrointestinal tract symptoms at Kenyatta National Hospital, Nairobi. *East Afr Med J* 2002; **79**: 226–231.
15 de Boer WA, Thys JC, Borody TJ *et al.* Proposal for use of a standard side effect scoring system in studies exploring *Helicobacter pylori* treatment regimens. *Eur J Gastroenterol Hepatol* 1996; **8**: 641–643.
16 Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 19th informational supplement. Clinical and Laboratory Standards Insitute, document M100-S19, 19th edn. Wayne, Pennsylvania, USA, Clinical and Laboratory Standards Institute.
17 Miendje Deyi VY, Bontems P, Vanderpas J *et al.* Routine survey determinations of resistance of *Helicobacter pylori* to antimicrobials over the last 20 years (1999 to 2009) in Belgium. *J Clin Microbiol* 2011; **49**: 2200–2209.
18 Dixon MF, Genta RM, Yardley JH *et al.* Classification and grading of gastritis. *Am J Surg Pathol* 1996; **20**: 1161–1181.
19 Graham YD, Lee S-Y. How to effectively use bismuth quadruple therapy: the good, the bad, and the ugly. *Gastroenterol Clin North Am* 2015; **44**: 537–563.
20 Graham DY, Dore MP. *Helicobacter pylori* therapy: a paradigm shift. *Expert Rev Anti Infect Ther* 2016; **14**: 577–585.
21 Nkuize M, De Wit S, Muls V *et al.* HIV-*Helicobacter pylori* co-infection: antibiotic resistance, prevalence, and risk factors. *PLoS One* 2015; **10**: e0145119.
22 Breslow NE, Day NE. Design considerations. Part 7. 6. Case-control sampling within a cohort. Statistical methods in cancer research, Vol. II: the design and analysis of cohort studies. IARC scientific publication n° 82. 1987. Lyon, IARC 1987, pp. 271–314.
23 Epi Info™, Division of Health Informatics and Surveillance (DHIS), Center for Surveillance, Epidemiology and Laboratory Services (CSELS), CDC – Centers for Disease Control and Prevention.
24 Yager J, Faragon J, McGuey L *et al.* Relationship between single tablet antiretroviral regimen and adherence to antiretroviral and non-antiretroviral medications among veterans' affairs patients with human immunodeficiency virus. *AIDS Patient Care STDS* 2017; **31**: 3706.
25 University of Liverpool. HIV drug interactions tool. https://www.hiv-druginteractions.org/checker.
26 Zhu L, Persson A, Mahnke L *et al.* Effect of low-dose omeprazole (20 mg daily) on phamacokinetics of multiple-dose atazanavir with ritonavir in healthy subjects. *J Clin Phamacol* 2011; **51**: 368–377.
27 Nachega JB, Hsu A, Uthman A *et al.* Antiretroviral therapy adherence and drug-drug interactions in the aging HIV population. *AIDS* 2012; **26**: S39–S53.
28 Feierman DE, Melinkov Z, Nanji AA. Induction of CYP3A by ethanol in multiple in vitro and in vivo models. *Alcohol Clin Exp Res* 2003; **27**: 981–988.
29 Franke A, Teyssen S, Harder H, Singer MV. Effect of ethanol and some alcoholic beverages on gastric emptying in humans. *Scand J Gastroenterol* 2004; **39**: 638–644.
30 Chey WD, Wong BCY. Practice Parameters Committee of the American College of Gastroenterology American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. *Am J Gastroenterol* 2007; **102**: 1808–1825.
31 Miendje Deyi VY, Vanderpas J, Bontems P *et al.* Marching cohort of *Helicobacter pylori* infection over two decades (1988–2007): combined effects of secular trend and population migration. *Epidemiol Infect* 2011; **139**: 572–580.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Treatment schedule proposed to patients.

Appendix S2. HAART composition in 201 HIV-positive individuals.

Appendix S3. Analysis restricted to the ST3 *H. pylori* treatment subcohort.

Appendix S4. *H. pylori* S3T eradication failure stratified by $CD4^+$ T count and by HAART use among 224 *H. pylori*-HIV-co-infected individuals.