Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

Research of the month (August 2015)
Clinical research

Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

Vaccine 33 (2015) 4820–4826

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Impact factor = 3.624

Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

W. Ratanasuwan[a], Y.H. Kim[b,*], B.K. Sah[b], S. Suwanagool[a], D.R. Kim[b], A. Anekthananon[a], A.L. Lopez[c], W. Techasathit[a], S.L. Grahek[d,e], J.D. Clemens[f], T.F. Wierzba[b]

[a] Siriraj Hospital, Mahidol University, Bangkok, Thailand
[b] International Vaccine Institute, Seoul, Republic of Korea
[c] University of the Philippines Manila – National Institutes of Health, Manila, Philippines
[d] The George Washington University School of Medicine and Health Sciences, Washington, DC, United States
[e] Sabin Vaccine Institute, Washington, DC, United States
[f] International Center for Diarrheal Disease Research, Dhaka, Bangladesh

ARTICLE INFO

Article history:
Received 27 March 2015
Received in revised form 21 July 2015
Accepted 23 July 2015
Available online 1 August 2015

Keywords:
Oral cholera vaccine
Peru-15
Live attenuated cholera vaccine
Immunogenicity
Safety
HIV-seropositive adult

ABSTRACT

Background: Many areas with endemic and epidemic cholera report significant levels of HIV transmission. According to the World Health Organization (WHO), over 95% of reported cholera cases occur in Africa, which also accounts for nearly 70% of people living with HIV/AIDS globally. Peru-15, a promising single dose live attenuated oral cholera vaccine (LA-OCV), was previously found to be safe and immunogenic in cholera endemic areas. However, no data on the vaccine's safety among HIV-seropositive adults had been collected.

Methods: This study was a double-blinded, individually randomized, placebo-controlled trial enrolling HIV-seropositive adults, 18–45 years of age, conducted in Bangkok, Thailand, to assess the safety of Peru-15 in a HIV-seropositive cohort.

Results: 32 HIV infected subjects were randomized to receive either a single oral dose of the Peru-15 vaccine with a buffer or a placebo (buffer only). No serious adverse events were reported during the follow-up period in either group. The geometric mean fold (GMF) rise in *V. cholerae* O1 El Tor specific antibody titers between baseline and 7 days after dosing was 32.0 ($p < 0.001$) in the vaccine group compared to 1.6 ($p < 0.14$) in the placebo group. Among the 16 vaccinees,14 vaccinees (87.5%) had seroconversion compared to 1 of 16 placebo recipients (6.3%). *V. cholerae* was isolated from the stool of one vaccinee, and found to be genetically identical to the Peru-15 vaccine strain. There were no significant changes in HIV viral load or CD4 T-cell counts between vaccine and placebo groups.

Conclusion: Peru-15 was shown to be safe and immunogenic in HIV-seropositive Thai adults.

© 2015 Elsevier Ltd. All rights reserved.

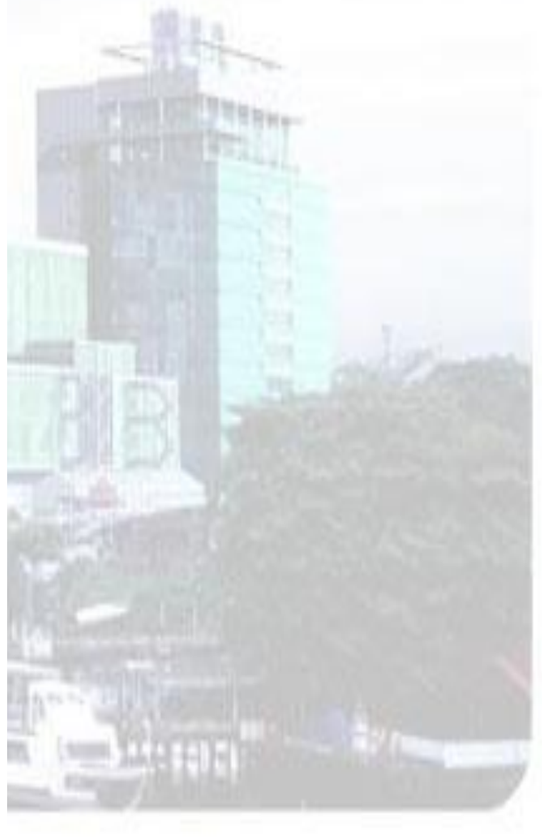
1. Introduction

Cholera is an acute watery diarrheal illness with an estimated 2.8 million cases and 91,000 deaths occurring annually in endemic countries [1]. Many areas with cholera transmission also report significant levels of HIV transmission, possibly due to similar predisposing socioeconomic factors including poverty and lack of education. Excluding the recent cholera outbreak in Haiti, over 95% of officially reported cholera cases to the World Health Organization (WHO) come from Africa, which also accounts for nearly 70% of total people living with HIV/AIDS globally [2–5]. Nearly two-thirds of cholera outbreak reports to ProMed came from Sub-Saharan Africa from 1995 to 2005 [6]. Additionally, a study in a cholera endemic area in Mozambique suggests that HIV infection is associated with an increased risk of cholera [7].

The WHO recommends that available oral cholera vaccines (OCVs) should be used in conjunction with other preventive and control strategies in cholera prone countries [8]. Currently available OCVs (Dukoral and Shanchol) are both composed of killed whole-cell, require at least two dose regimens, and are not licensed for use in infants. While Dukoral has been shown to be safe and immunogenic in HIV infected individuals [9], there is no similar data for

* Corresponding author at: International Vaccine Institute (IVI) SNU Research Park, San 4-8 Nakseongdae-dong, Kwanak-gu, Seoul 151-919, Republic of Korea. Tel.: +82 2 881 1366; fax: +82 2 881 1164.
E-mail address: yhkim@ivi.int (Y.H. Kim).

http://dx.doi.org/10.1016/j.vaccine.2015.07.073
0264-410X/© 2015 Elsevier Ltd. All rights reserved.



Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

Assoc.Prof.Dr. Winai Ratanasuwan
Department: Preventive and social medicine
Field of interests: Infectious diseases and immune deficiency
Contribution: First author

Prof.Dr. Surapol Suwanagool
Department: Preventive and social medicine
Field of interests: Infectious diseases and immune deficiency
Contribution: Co-author

Assist. Prof.Dr. Wichai Techasathit
Department: Preventive and social medicine
Field of interests: Infectious diseases and immune deficiency
Contribution: Co-author

Assist. Prof.Dr. Thanomsak Anekthananon
Department: Preventive and social medicine
Field of interests: Infectious diseases and immune deficiency
Contribution: Co-author

Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

Table 1 : Baseline characteristics.

	Vaccine group ($n = 16$)	Placebo group ($n = 16$)	p-value
Sex			
n (%) of male	3 (18.8%)	7 (43.8%)	0.25
n (%) of female	13 (81.3%)	9 (56.3%)	
Age (years)			
Mean (sd)	37.3 (4.2)	38 (3.1)	0.61
Median (min, max)	37 (26.3, 43.1)	37.4 (32.7, 44.2)	
HAART			
n (%) of HAART	14 (87.5%)	14 (87.5%)	1.00
n (%) of no HAART	2 (12.5%)	2 (12.5%)	
HAART duration (years)			
Mean (sd)	8.6 (3.5)	7.4 (3.1)	0.25
Median (min, max)	10 (1, 12)	7 (2, 12)	
CD4 T-cell count (cells/mm^3)			
Mean (sd)	787.5 (287.9)	716.3 (165.6)	0.78
Median (min, max)	730 (506, 1638)	665 (516, 1074)	
CD4 T-cell count (cells/mm^3) (category)			
500–≤1000	14 (87.5%)	15 (93.8%)	1.00
>1000	2 (12.5%)	1 (6.3%)	
HIV-1 RNA levels (copies/mL)			
Mean (sd)	670.9 (1825.7)	465.1 (1687.1)	1.00
Median (min, max)	20 (20, 6356)	20 (20, 6783)	
HIV-1 RNA levels (copies/mL); category			
<40	14 (87.5%)	14 (87.5%)	1.00
40–<10,000	2 (12.5%)	2 (12.5%)	

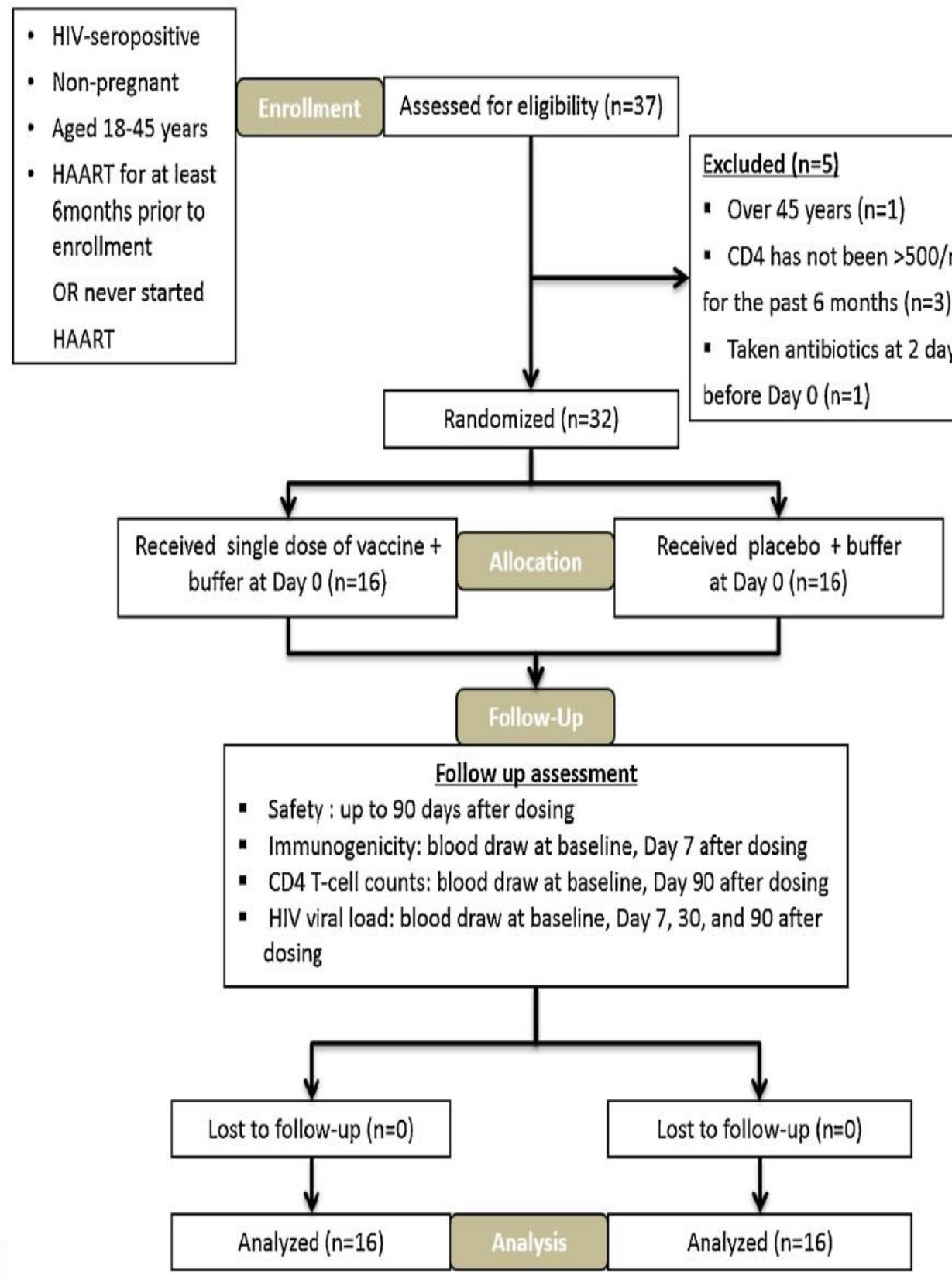
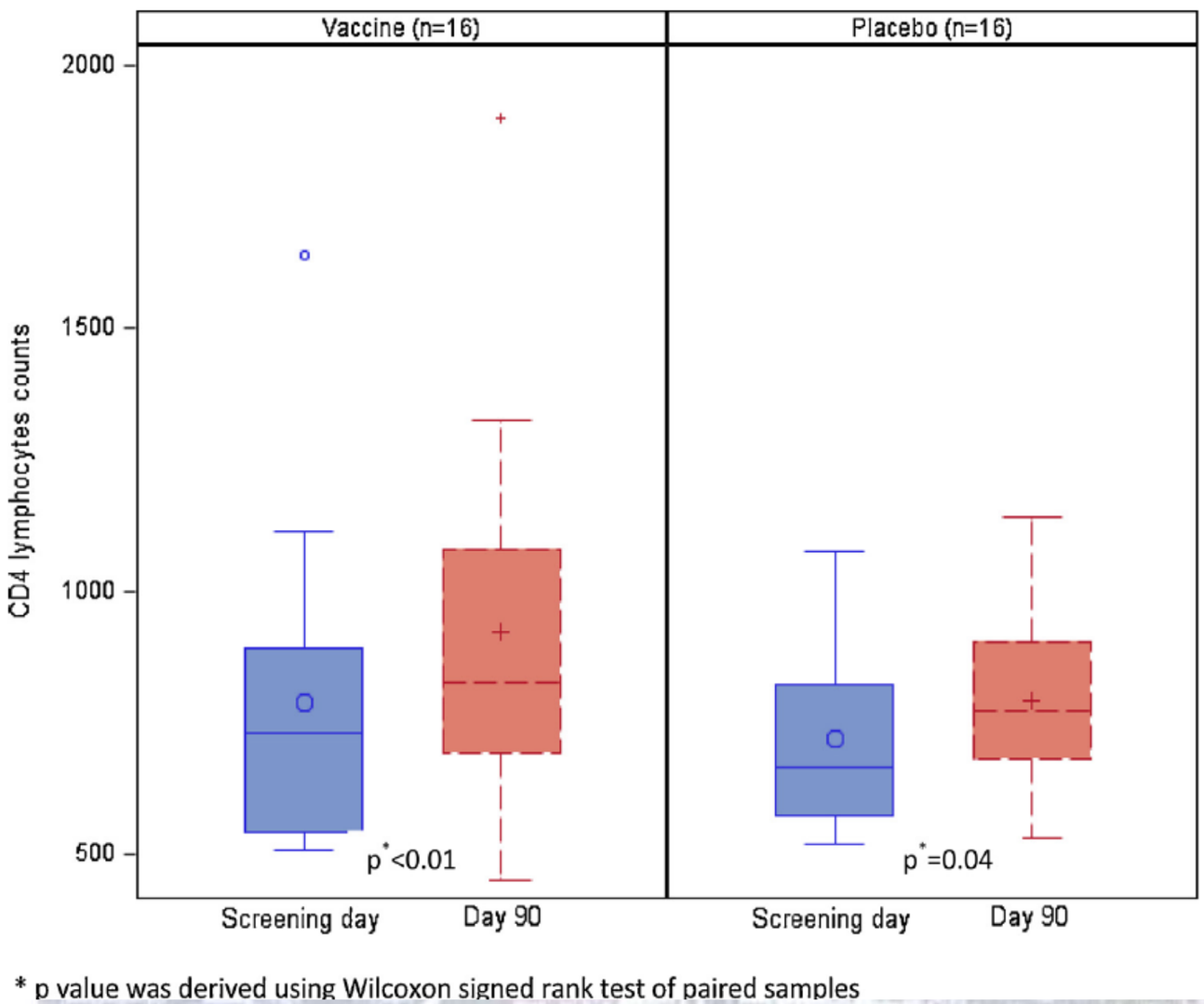


Fig. 1 : Consort flow diagram.

Peru-15 (Choleragarde®), a live attenuated oral cholera vaccine, is safe and immunogenic in human immunodeficiency virus (HIV)-seropositive adults in Thailand

Table 2 : Adverse events following dosing.

N (%)	Vaccine group (*N* = 16) All grade	Placebo group (*N* = 16) All grade	*p*-value All grade
Within 7 days following dosing			
Gas	10 (62.5%)	9 (56.3%)	0.72
Nausea	2 (12.5%)	1 (6.3%)	1.00
Headache	3 (18.8%)	1 (6.3%)	0.60
Vomiting	0	0	–
Abdominal Cramps	3 (18.8%)	0	0.23
Myalgias	2 (12.5%)	0	0.48
Diarrhea	2 (12.5%) [32.7%][a]	1 (6.3%)	1.00
Fever	0	0	–
Number (%) of subjects with ≥1 solicited AEs within 7 days following dosing	13 (81.3%) [56.3%][a]	9 (56.3%)	0.25
Number (%) of subjects with ≥1 solicited AEs OR unsolicited AEs within 90 days following dosing	14 (87.5%)	9 (56.3%)	0.11



* p value was derived using Wilcoxon signed rank test of paired samples

Fig. 2 : Boxplot of Cd4 lymphocytes counts at screening and day 90.

Table 3 : Serum vibriocidal antibody titers (at baseline, 7 days after dosing).

	Vaccine group (*n* = 16)	Placebo group (*n* = 16)	*p*-value
Baseline			
GMT[a] (95% CI)	30.8 (14.8, 64.5)	19.2 (8.4, 43.7)	0.70
7 days after dosing			
GMT[a] (95% CI)	987 (503.7, 1934)	30.8 (11.0, 86.8)	<0.01
GMF[b] rise (95% CI)	32 (11.8, 87)	1.6 (0.6, 4.1)	<0.01
Number (%) of subjects who seroconverted[c]	14 (87.5%)	1 (6.3%)	<0.01