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Factors Associated with Improved HIV/AIDS Treatment Outcomes: Comparing two Major ART Service Delivery Models in Vietnam

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Abstract
A mixed design approach was performed to assess the CD4 count levels over time and their associated factors among 362 HIV patients on ART from clinics with HIV testing and counseling (ART-HTC) services and those with general healthcare (ART-GH) services. Longitudinal CD4 count data were retrospectively collected from medical records. Sociodemographic, clinical, alcohol use and smoking characteristics were obtained via face-to-face interviews. Multivariate mixed effect linear regression was utilized to determine the association. We found that HIV patients at ART-GH clinics were more likely to achieve higher CD4 counts over time compared to patients at ART-HTC clinics. Additionally, having an increase in CD4 counts was found to be associated with having longer duration of ART and higher baseline CD4 levels. Cigarette smoking and hazardous alcohol use, however, were not associated with CD4 count improvement. Our findings suggest that combining HTC and GH services might provide a synergistic benefit in ART treatment outcomes through an improved access to comprehensive HIV healthcare services for HIV patients on therapy.

Keywords ART service delivery models · HIV testing and counseling services · HIV treatment outcome · Cigarette smoking · Alcohol use

Introduction

In the past two decades, extraordinary efforts have been made towards the elimination of the global HIV/AIDS epidemic [1]. In 2017, it was estimated that among 31.6 million people living with HIV (PLWH), more than 21.7 million of them were able to access antiretroviral therapy (ART) [2]. Moreover, the number of new HIV infections and AIDS-related deaths diminished by 47% and 51%, respectively, compared to the peaks in 1996 and 2004 [2]. In particular, Vietnam has achieved tremendous progress in this area thanks to its nationwide provision of ART services to 122,439 HIV patients out of 208,371 PLWH by September 2017 [3]. To date, this scaling-up is mainly under the financial support of external donors, such as the President's Emergency Plan For AIDS Relief (PEPFAR) and the Global Fund [3, 4]. However, the evolution of Vietnam's economy—from low to low-middle income country—has led to a rapid cut of these funding sources in coming years, requiring more substantial domestic investments from the Vietnamese government. This transition raises an urgent need of empirical evidence about the cost effectiveness and efficacy of existing ART service delivery models—information that would be vital for optimizing the resource allocation in HIV/AIDS response in Vietnam.

In Vietnam, there are two main models of ART service delivery: stand-alone and integrated facilities. Stand-alone

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facilities, such as provincial AIDS centers, only deliver HIV-related services, particularly ART and HIV testing and counseling (HTC) [5]. Integrated facilities, such as central/provincial/district general hospitals and district health centers, deliver both HIV-related and general health care (GH) services [5]. Regarding the operational costs between the two models, a previous study in 21 HIV treatment facilities found that non-ART costs at the stand-alone model were 44% higher than those at the integrated model [5]. Nonetheless, the efficacy of both models remains largely unexplored. One study found that PLWH or individuals with high risk of HIV infections perceived that they had greater privacy when using services in the stand-alone model, potentially due to the fact that most patients at such facilities were also living with HIV [6]. Moreover, healthcare professionals in this model can often spend more time with their patients than those at the integrated facilities, potentially increasing the quality of the services provided [5]. In contrast, both PLWH and patients with other health issues use services at the integrated facilities, which might result in PLWH having a greater fear of stigma, and subsequently poorer treatment outcomes among PLWH [7, 8]. Furthermore, although HIV has become a manageable chronic condition given recent advances in HIV treatments, PLWH on ART still have to face the increasing burden of aging and non-communicable diseases [9–11]. Therefore, the integrated model having both HIV-related and GH services might provide PLWH with treatment and care more promptly and comprehensively compared to the stand-alone model.

In this study, we aimed to compare the efficiency of the two major ART service delivery models, ART-HTC and ART-GH, in terms of CD4 cell counts over time as a marker of immunological treatment outcome, and explored the associated factors among general HIV patients at two HIV epicenters in Vietnam. We hypothesized that patients at ART-GH clinics (integrated model) would have better treatment outcomes than those at ART-HTC clinics (stand-alone model). With the expected decrease in international funding for HIV/AIDS programs, a greater knowledge of the potential factors underlying the improved treatment outcomes in primary ART service delivery models should help focus the available funding and guide implementation strategies for both HIV and substance control programs in Vietnam and other resource-limited settings [12–15].

Methods

Study Setting and Sampling Method

Data were collected from July to September 2017 at four outpatient clinics in Hanoi and Thanh Hoa, which are the two epicenters affording HIV/AIDS treatment services in Northern Vietnam as described (Table 1). Well-trained researchers recruited patients with confirmed HIV diagnoses using a convenience sampling method. A total of 362 patients/482 patients (75.1%) were included into the study according to the following eligibility criteria: (1) being 18 years old or above (2) consenting to participate in the study (3) having initiated ART at aforementioned clinics (4) having CD4 count data, and (5) being available for interview during the data collection period.

Briefly, after the participant received consultation or medications per the standard of care for PLWH, s/he was invited by the researchers into a small counseling room with restricted access and provided detailed information on the purpose, benefits, and risks of the study. In addition to the protection of their confidentiality, all participants signed written informed consents, acknowledging their full understanding of the study, participation and discretion to withdraw from the study at any time without affecting their current ART. The study protocol was approved by the Institutional Review Board of the Hanoi Medical University.

Study Design, Measures and Instruments

In order to examine the relationship between the change of CD4 cell counts and current alcohol use and smoking in two ART delivery models, we utilized a mixed method approach [16] that includes two main components: a longitudinal

Table 1 Study settings and sample size

Geographic level	Location	Site name	ART service delivery model	Number of health professionals	Number of patients managed	Number of patients recruited
Province (urban)	Thanh Hoa	Provincial HIV/AIDS Control Centre	ART-HTC	5	141	135
District (rural)	Hanoi	Ung Hoa District Health Center	ART-HTC	3	103	92
District (mountainous)	Thanh Hoa	Quang Xuong General Hospital	ART-GH	3	41	37
District (mountainous)	Hanoi	Ba Vi General Hospital	ART-GH	4	101	98
		Total			482	362

HTC HIV testing and counseling service, *ART* antiretroviral treatment, *GH* general healthcare

assessment of CD4 cell counts and a cross-sectional survey among patients receiving ART at the selected clinics.

Primary Outcome

CD4 cell count data, extracted from medical records of the participants over the course of ART until the date of interview, were used as an indication of HIV immunological treatment outcome. In Vietnam, CD4 count testing is conducted every 6 months. In this study, the fewest number of CD4 testing time was one time, and the highest was 11 times (Fig. 1).

Socioeconomic Characteristics

Using structured questionnaires in face-to-face interviews, socio-economic data, including gender, age, education level, and current occupation, were obtained.

Clinical Characteristics

Participants were asked to report their HIV infection stages, comorbidities, and ART treatment duration. Moreover, adherence to ART in the last month was self-reported by using a visual analog scale (VAS), which ranges from 0 (complete non-adherence) to 100-point (complete adherence) [17–20].

Alcohol Misuse

The alcohol use disorders identification test-consumption (AUDIT-C) was used to screen for current alcohol misuse [21]. There are three questions in this instrument with scores raging from 0 to 4, resulting in a total score of 0–12. The higher the AUDIT-C score, the more likely the participants had hazardous alcohol drinking or active alcohol use disorders, including alcohol abuse or dependence. Male patients with a score of 4 or above and female patients with a score of 3 or above were considered AUDIT-C positive, or hazardous drinkers [21].

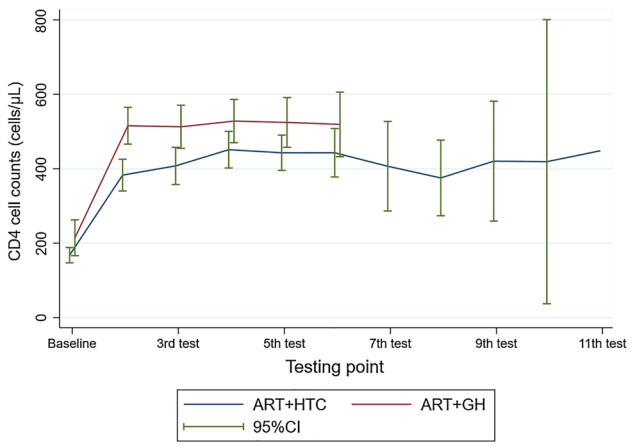

Fig. 1 Improvement of CD4 cell count (cells/μL) over different testing points between two service delivery models, ART-HTC and ART-GH. *ART* antiretroviral therapy, *HTC* HIV testing and counseling, *GH* general health care, *CI* confident interval

Cigarette Smoking

Participants were asked to estimate the number of cigarettes they ever smoked in their lifetime, as well as report whether they had smoked in the last 30 days. Patients who smoked more than 100 cigarettes and those who smoked in the last 30 days until the interview were categorized into "current smoker". Meanwhile, those who smoked more than 100 cigarettes in their lifetime, but did not smoke in the last 30 days, were identified as "former smoker". Other patients, who did not belong to these two groups, were identified as "no smoking". Of note, the 12 patients who were classified as "former smoker" were grouped into the "ever smoking" category. For current smokers, we also asked them to report the number of cigarettes smoked per day.

Statistical Analysis

Data were analyzed by STATA version 12 (Stata Corp. LP, College Station, USA). A p-value of log likelihood ratio test < 0.05 was considered statistically significant. We examined the associations between CD4 count over time and different service delivery models by employing the multivariate mixed effect linear regression with subject-specific random intercepts and slopes to account for within subject correlation. In the first statistical model, we tested the main hypothesis that CD4 cell count among patients in ART-GH (integrated) model were significantly higher than those in ART-HTC (stand-alone) model (model 1). In model 2, we adjusted for age, gender, ART adherence (VAS), duration of ART, baseline CD4 count, smoking status and AUDIT-C positive as potential confounders. Of note, Spearman correlation coefficients were calculated prior to regression modeling for all independent variables and covariates (all correlations $r < 0.40$, of which baseline CD4 cell count had the highest correlation with rho $= 0.3168$).

Results

Of the 362 participants, 62.7% of them enrolled in ART clinics offering HTC services (ART-HTC) (Table 2); 64.4% of the participants were male, and 49.7% of them were in the age groups 30—under 40 years old. The majority of participants had completed education that was below the high school level (64.2%), and most reported their occupation

Table 2 Sociodemographic characteristics of participants

Characteristics	ART-HTC		ART-GH		Total		p-value
	N	%	N	%	N	%	
Gender							
Male	145	63.9	88	65.2	233	64.4	0.80
Female	82	36.1	47	34.8	129	35.6	–
Age groups							
Below 30 years	31	13.7	14	10.4	45	12.4	0.35
30- < 40 years	118	52.0	62	45.9	180	49.7	–
40- < 50 years	56	24.7	42	31.1	98	27.1	–
50 years and above	22	9.7	17	12.6	39	10.8	–
Education attainment[a]							
Below high school	133	58.9	98	73.1	231	64.2	< 0.01
High school	77	34.1	35	26.1	112	31.1	
Above high school	16	7.1	1	0.8	17	4.7	
Occupations							
Unemployed	15	6.6	24	17.8	39	10.8	< 0.01
Self-employment	157	69.2	69	51.1	226	62.4	–
Blue-workers/farmers	38	16.7	35	25.9	73	20.2	–
Others	17	7.5	7	5.2	24	6.6	–
Total	227	62.7	135	37.3	362	100.0	–

ART antiretroviral therapy, *HTC* HIV testing and counseling service, *GH* general health care

[a]One participant did not report the education attainment

as self-employment (62.4%). Between the two ART service delivery models, significant differences in the education attainment and occupations were observed ($p < 0.01$). In particular, 58.9% of participants in ART-HTC clinics had completed lower than a high school education level compared to 73.1% among the participants in ART-GH clinics, and the unemployment rate in ART-HTC clinics was 6.6% compared to 17.8% in ART-GH clinics.

Figure 1 shows the improvement of CD4 cell count overtime between participants at ART-HTC and ART-GH clinics. Clinically, most participants in our cohort exhibited an increase in CD4 count over time (90.6%) with the average CD4 cell counts at the time of treatment initiation and at the latest CD4 testing being 182.9 ± 190.6 and 455.0 ± 243.5 cells/μL, respectively (Table 3). Overall, the majority of participants had also achieved the asymptomatic HIV infection stage (56.9%) in which 37.9% of participants reported having comorbidities, including HIV-associated ones, e.g. cardiovascular and respiratory diseases. Between the two ART service delivery models, we observed a difference in the HIV stages ($p < 0.01$). Particularly, 41.1% of the participants in the ART-HTC clinics achieved an asymptomatic stage compared to 82.2% in ART-GH clinics. Notably, participants in the ART-HTC clinics were on ART longer than those in ART-GH with the average duration of 3.7 ± 2.6 years on ART (4.0 ± 2.7 vs. 3.3 ± 2.3 years, respectively, $p = 0.01$). In addition, participants receiving HTC services reported having higher medication adherence to ART, as assessed by VAS score, compared to ones at GH clinics (89.5 ± 15.5 vs. 87.8 ± 9.6, respectively, $p < 0.01$). No differences were found in the presence of comorbidity or baseline CD4 count of the participants between the two clinics ($p = 0.32$ and 0.84, respectively). However, participants in ART-HTC clinics achieved lower CD4 counts at their latest visits compared to patients at GH clinics (416.5 ± 241.0 vs. 519.6 ± 234.8 cells/μL, respectively, $p < 0.01$). Regarding hazardous alcohol use, 30.4% of all participants identified as having a positive AUDIT-C with the average AUDIT-C score of 2.2 ± 2.8. In addition, we observed a high prevalence of participants (50.6%) who reported to have ever smoked with 10 ± 6.9 cigarettes per day on average, irrespective of the type of ART delivery service models. No differences in the alcohol misuse AUDIT-C score and number of cigarettes smoked per day were found between the two ART service delivery models ($p = 0.94$ and 0.32, respectively).

In both unadjusted and adjusted models (Table 4), participants at ART-GH clinics had higher CD4 cell counts over time compared to those at ART-HTC clinics (Model 1: Coef. = 120.96, 95% CI 74.59–167.34, and Model 2: Coef. = 81.10, 95% CI 39.67–122.53, $p < 0.01$). In the adjusted model, being older and male patients were associated with having lower CD4 cell counts overtime. In addition, we found that increasing CD4 count over time was positively associated with longer duration of ART (Coef. = 18.04; 95% CI 10.38–25.70, $p < 0.01$), and higher baseline CD4 count (Coef. = 0.73; 95% CI 0.63–0.84,

Table 3 Clinical characteristics of participants

Characteristics	ART-HTC		ART-GH		Total		p-value
	N	%	N	%	N	%	
HIV stages							
Asymptomatic	90	41.1	111	82.8	201	56.9	< 0.01
Symptomatic	29	13.2	11	8.2	40	11.3	–
AIDS	15	6.9	2	1.5	17	4.8	–
Unknown	85	38.8	10	7.5	95	26.9	–
Comorbidities							
Yes	85	37.4	52	38.5	137	37.9	0.84
No	142	62.6	83	61.5	225	62.2	–
Alcohol misuse, AUDIT-C							
Positive[a]	63	27.8	47	34.8	110	30.4	0.16
Negative	164	72.3	88	65.2	252	69.6	–
Ever smoking							
Yes	111	48.9	72	53.3	183	50.6	0.41
No	116	51.1	63	46.7	179	49.4	–
Trend in CD4 cell count (baseline to current level)							
Decrease	26	11.5	8	5.9	34	9.4	0.08
Increase	201	88.6	127	94.1	328	90.6	
	Mean	SD	Mean	SD	Mean	SD	
Duration of ART (years)	4.0	2.7	3.3	2.3	3.7	2.6	0.01
Baseline CD4 cell counts (cells/μL)[b]	167.8	154.6	214.5	247.6	182.9	190.6	0.32
Current CD4 cell count (cells/μL)[c]	416.5	241.0	519.6	234.8	455.0	243.5	< 0.01
ART adherence VAS score	89.5	15.5	87.8	9.6	88.9	13.6	< 0.01
Alcohol misuse AUDIT-C score	2.1	2.7	2.3	3.0	2.2	2.8	0.94
Number of cigarettes per day (n = 183)	9.7	7.0	10.5	6.8	10.0	6.9	0.32

ART antiretroviral therapy, *HTC* HIV testing and counseling service, *GH* general health care

[a]AUDIT-C score ≥ 3 for women and ≥ 4 for men suggests potential hazardous alcohol drinking, or active alcohol use disorders

[b]CD4 cell counts at the time of initiating ART

[c]CD4 cell count at the latest test

$p < 0.01$). We did not find a relationship between hazardous alcohol use and smoking status with CD4 cell count overtime.

Discussion

This study assessed the differences in HIV treatment outcomes between two major ART delivery service models in Vietnam: stand-alone (ART-HTC) and integrated (ART-GH) models. We found that HIV patients receiving ART at clinics affording only HTC services performed worse than patients at the GH clinics in terms of CD4 count improvement. Moreover, we identified several potential drivers for such improvement, including the patient age, gender and baseline CD4 cell counts. Further studies are warranted to explore the potential benefit of combining HTC and GH services to improve the efficacy of ART services for PLWH in Vietnam.

Previous studies have indicated that incorporating HTC services into ART clinics might facilitate earlier diagnosis and treatment initiation for PLWH [22]. Nonetheless, we observed that PLWH receiving ART services at ART-GH clinics (the integrated model) still outperformed their counterparts in terms of CD4 count improvement. Given the potential health complications from long-term ART use, HIV co-infections, and non-HIV/AIDS-related illnesses, our finding might be explained by the fact that ART clinics with GH services could promptly provide a wider range of medical care services, especially for patients with additional burdens of substance abuse [14, 23–26]. For example, a prospective study at multiple clinical centers in the US found that having a poor HIV treatment outcome, including lower CD4 counts, was associated with patient's nonattendance early in the study, and lack of access to primary healthcare services and insurance were among factors associated with nonattendance at later study visits [27]. Moreover, HIV

Table 4 Unadjusted and adjusted models of CD4 cell counts over time in HIV patients

Characteristics	Unadjusted model (Model 1)		Adjusted model (Model 2)	
	Coef.	95% CI	Coef.	95% CI
Service delivery models				
ART-HTC	Ref	–	–	–
ART-GH	120.96**	74.59; 167.34	81.10**	39.67; 122.53
Age groups				
< 30 years	–	–	Ref	–
30- < 40 years	–	–	− 50.54	− 114.26; 13.18
40- < 50 years	–	–	− 46.96	− 114.64; 20.73
50 years and above	–	–	− 84.45*	− 167.09; − 1.81
Gender				
Female	–	–	Ref	–
Male	–	–	− 81.19**	− 138.52; − 23.85
Hazardous drinking[a]				
No	–	–	Ref	
Yes	–	–	35.39	− 8.72; 79.50
Ever smoking				
No	–	–	Ref	–
Yes	–	–	27.42	− 26.16; 81.00
ART Adherence VAS score	–	–	1.31	− 0.07; 2.69
Duration of ART (years)	–	–	18.04**	10.38; 25.70
Baseline CD4 cell count[b]	–	–	0.73**	0.63; 0.84

ART antiretroviral therapy, *HTC* HIV testing and counseling service, *GH* General health care

*p < 0.05; **p < 0.01

[a]Yes indicates AUDIT-C+

[b]CD4 cell counts at the time of initiating ART

patients in ART-HTC clinics might have to take more time to be referred in order to obtain medical treatments despite having a better access to HIV treatment and counseling services [15, 28]. In fact, the World Health Organization has underlined the importance of integrative models, including a number of services, such as ART, methadone maintenance treatment and general health care services, in the treatment of HIV, especially for patients who also inject drugs [29]. In our study, with comparable comorbidity, baseline CD4 level and substance use pattern between the two ART delivery models, it is thus plausible that enhancing the integration of HTC and GH services into HIV care and support programs in the delivery of ART might facilitate a more comprehensive and timely management of the various healthcare needs of HIV patients.

The potential impact of alcohol dependence and cigarette smoking on worsening HIV treatment outcomes, including CD4 count decline, have been documented among HIV patients in Vietnam and other countries [26, 30–35]. In our study, where the majority of participants had achieved the asymptomatic stage of HIV with a low presence of comorbidities and an overall increasing trend in CD4 count, it might not be surprising that we did not find an association between cigarette smoking or hazardous alcohol use and such trend in CD4 count over time. In fact, unhealthy alcohol consumption has been shown to exert no apparent effect on short-term CD4 count decline in ART-naïve HIV patients from a longitudinal study in Uganda [36]. A similar observation has also been found in other studies with evidence suggestive of an effect of hazardous alcohol consumption on CD4 decline through ART adherence [37–39]. Interestingly, among other factors, the high effectiveness of ART on immune reconstitution, especially when ART is initiated early and sufficient ART adherence is maintained, might compensate for the negative effect of alcohol—when consumed at a low level—on CD4 counts among HIV-infected patients [38, 40]. Similar to alcohol use, we did not find any association between smoking and CD4 counts improvement. In the literature, the impact of cigarette smoking on CD4 count has been shown to vary over the course of HIV treatment [41–44]. By the same token, owing to a great heterogeneity of study designs and populations, the impact of various types and levels of cigarette smoking and alcohol consumption on HIV treatment and disease outcomes might not be consistently detected at variable levels of CD4 count and adherence to ART regimens over time across studies [26, 32, 36, 38, 41, 45–48]. Nonetheless, given the well-demonstrated benefit of ART,

it is important to note that the potential negative effects of cigarette smoking and alcohol consumption on HIV infection and AIDS treatment and management should not justify withholding ART initiation from HIV patients with substance use problems. Rather, given a high prevalence of alcohol use and smoking as observed in our sample, continued effort to increase the availability and access to substance abuse screening, counseling, and education should be made for patients receiving HIV treatments regardless of ART service delivery model.

Lastly, it has been shown that ART adherence is strictly required for an optimal HIV treatment outcome regardless of service delivery models [49]. In this study, our regression model found no relationship between adherence and CD4 cell counts improvement. When we attempted to explore the association between ART service models and adherence, we also did not find any correlation (data not shown). This observation might be due to the homogeneity of our sample regarding adherence. Nonetheless, our finding that patients with higher baseline CD4 cell counts were more likely to achieve higher CD4 cell counts overtime is in agreement with the recommendation of early ART initiation for PLWH [50].

Our study faces several limitations. First, the lack of random assignment of patients alone might contribute to the differences observed in their sociodemographic and clinical characteristics among the participants between the two ART delivery models. Moreover, the relatively small sample size through a convenience sampling approach might further limit the generalizability of our results to all patients, such as those who had not yet engaged in HIV care. The large proportion of patients in the ART-HTC model with unknown information about HIV stage might also lead to bias in estimating the CD4 cell counts improvement. Lastly, despite our application of the most widely used tests for substance use and ART adherence, a potential recall bias from self-report data might also affect our results.

In conclusion, our study provides initial evidence suggesting that patients receiving ART at the ART-GH clinics under the integrated model had better CD4 cell count over time than those at the ART-HTC clinics under the standalone model. Following the expected decrease in international funding for HIV programs, the development of a more synchronized HIV and substance use management for HIV patients on ART is needed. Future studies examining the effectiveness of such integrative ART adherence treatment model should be carried out in order to fully operationalize such model within the existing healthcare structure in Vietnam.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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