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Cost-Effectiveness of Antiretroviral Therapy Expansion Strategies in Vietnam

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Abstract

This study determines an optimal strategy for scaling up ART in Vietnam by examining three initiation thresholds [350 cells/mm^3, 500 cells/mm^3, and treat all people living with HIV (PLHIV) regardless of CD4 cell counts] and treatment commencement rates among treatment-eligible PLHIV ranging from 5% to 100% within 12 months of diagnosis. Incremental cost-effectiveness ratios (ICERs) were calculated using a Markov model, based on data from a cohort of 3449 patients who initiated ART between January 1, 2005 and December 31, 2009 in 13 outpatient clinics across six provinces in Vietnam. Our analyses indicated that raising treatment eligibility criteria, in line with WHO guidelines (CD4 $\leq$500 cells/mm^3) or removing CD4-based criteria would both be cost-effective in Vietnam. However, the cost-effective strategy from an economic viewpoint is first to increase coverage substantially among those with lowest CD4 levels, and only when coverage increases towards saturation should initiation criteria be lifted. Universal coverage under current guidelines would cost an additional $85 million and $96 million per year if the treatment threshold was 500 cells/mm^3. These scenarios would avert 15,000 and 22,000 HIV-related deaths in 2010–2019, with ICERs of $500–$660 per QALY gained. It is imperative to increase treatment coverage for newly diagnosed PLHIV in Vietnam according to the current guidelines prior to increasing the CD4 threshold for ART initiation.

Introduction

Antiretroviral therapy (ART) has been shown to be effective in reducing HIV-related mortality and morbidity, and improving the quality of life of HIV patients.[1–4] In Vietnam, ART was first commenced in three clinics in Hanoi and Ho Chi Minh City in 2004. With international funding from the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR), the number of ART sites expanded to 74 by 2005 and to 320 by 2011, covering all 64 Vietnamese provinces and cities. In addition to increasing the number of sites, the availability of ART was further increased in 2010 when Vietnam adopted the World Health Organization (WHO) recommendation to initiate ART when CD4 cell count $\leq$350 cells/mm^3, replacing the previous threshold of 200 cells/mm^3. By 2012, cumulatively 263,317 HIV cases had been reported in Vietnam, of whom 69,291 adults and 3,701 children were receiving ART.[5,6]

In July 2013, WHO launched its new HIV treatment guidelines, recommending ART be initiated at a CD4 cell count $\leq$500 cells/mm^3, largely in response to published cohort studies and mathematical modeling from Europe and the US showing that more optimal treatment outcomes would be obtained if ART was initiated at this higher CD4 cell count level.[3,7–9] Increasing ART treatment initiation threshold to CD4 cell count $\leq$500 cells/mm^3 was also shown to be cost-effective.[8,10–14]

Nevertheless, the question of whether this higher WHO threshold is applicable in resource-poor settings that typically have limited treatment resources but high demand for ART remains a subject of debate. In the US, for example, initiating ART when CD4 cell count is $>$350 cells/mm^3 would result in an estimated incremental cost-effectiveness ratio (ICER) of US $31,266 per quality-adjusted life-year (QALY), which is less than UA $50,000 per QALY gained, and is considered cost effective.[8] In South Africa, however, increasing ART initiation from a CD4 cell count threshold of 350 cells/mm^3 to 500 cells/mm^3 would result in an estimated ICER of US $1137 per QALY which, at more than three times South Africa's gross domestic product per capita (GDPPC),[15,16] is

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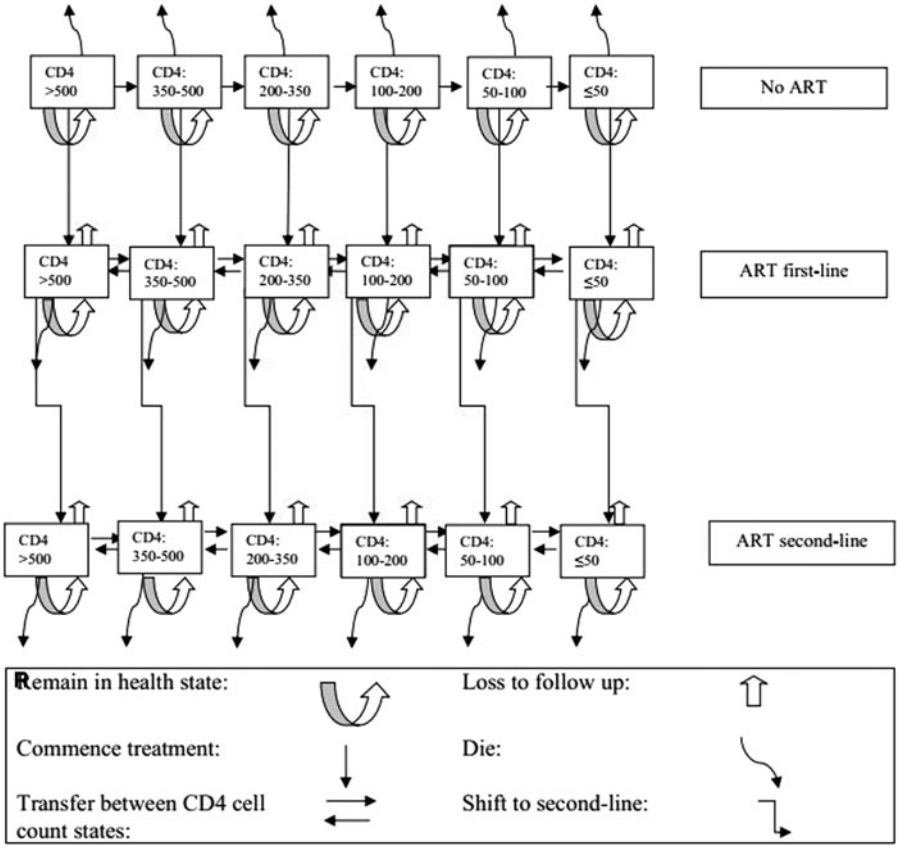

FIG. 1. State transition diagram of the Markov model.

not cost-effective following WHO's definition of three times the per capita GDP (ICER is ≤1 GDPPC, very cost effective; 1 GDPPC < ICER ≤3 GDPPC, cost effective; ICER > 3 GDPPC, not cost effective). In Vietnam, one study showed that upgrading CD4 cell count threshold to 500 cells/mm^3 or treating all PLHIV would be cost effective.[17] However, upgrading treatment threshold has challenges, particularly in a poor resource setting, including capacity building, task shifting, and treatment retention.[18]

An alternative method of improving the cost-effectiveness of ART in developing countries is to improve treatment commencement rates. Increasing ART coverage to universal access, for example, achieved net cost savings in Swaziland and Cameroon.[19] In the Ukraine, increasing ART initiation to 80% of eligible people living with HIV (PLHIV) (that is, those with a CD4 cell count ≤350 cells/mm^3) was estimated to have achieved 105,000 additional QALYs, at US $1120 per QALY gained, relative to no intervention.[20] Improving treatment commencement rates, however, can be difficult to achieve in practice, particularly in source-limiting setting. Low capacity, lack of awareness, fear, and stigma are deterrent factors to HIV testing and treatment.[21] In Vietnam, for example, only an estimated 53% of PLHIV in Vietnam had access to ART and, among those currently receiving ART, 59% sought treatment at a late stage of disease progression.[22,23]

Provision of ART in Vietnam currently costs an estimated US $33.4 million.[24,25] There is an important question about whether it would be more cost-effective for Vietnam to improve ART treatment outcomes by increasing ART initiation threshold to a CD4 cell count ≤500 cells/mm^3 or treating all PLHIV regardless of CD4 cell counts at ART initiation versus by increasing the number of PLHIV accessing ART at the current threshold. This study will be the first to determine an optimal strategy for scaling up the availability of ART in Vietnam between 2010 and 2019. Specifically, it aims to quantify the cost-effectiveness of three initiation thresholds (350 cells/mm^3, 500 cells/mm^3, and treat all PLHIV regardless of CD4 cell counts) and treatment rates ranging from 5% to 100% within 12 months of diagnosis.

Methods

Study design and sample size

The ICERs were computed using a Markov model, populated by data from a cohort of 3449 patients who initiated ART between January 1, 2005 and December 31, 2009 in 13 outpatient clinics across six provinces in Vietnam. Details of the selected patients and clinics have been described elsewhere.[22] CD4 count at ART initiation (baseline) was defined as the latest CD4 level measured within 3 months prior to ART initiation. CD4 count at year one was defined as the latest CD4 level measured within 1 year after ART initiation.

Model structure and assumptions

A Markov state transition model was developed in TreeAge.[26] The model tracked a cohort of simulated individuals living with HIV infection over a period of 10 years. The model follows six health states, defined by their CD4 cell

count (> 500; 350–500; 200–350;100–200; 50–100; and <50 cells/mm^3). Patients entering the model either had, or had not, initiated ART. The initial distribution of the patients at various CD4 categories was previously determined.[22] Patients who had not initiated ART would: (1) stay in their current CD4 category, (2) transit to a lower CD4 cell category, (3) initiate ART, or (4) die. These patients were assumed not to be able to move to a higher CD4 category. Individuals who had initiated ART followed similar paths, but may move to lower CD4 categories due to treatment failure and shift to second-line therapy, or moved to higher CD4 category because of treatment efficacy.

Patients on second-line ART may stay at their CD4 category, move up or down a CD4 category, be lost to follow up, or die. Given the higher-line therapy is unavailable in Vietnam, patients who failed second-line ART were assumed to leave treatment. The model structure is presented in Fig. 1.

Data collection and model parameters

The health utilities and transition probabilities between various health states are summarized in Supplementary Table S1 (supplementary material is available online at www.liebertpub.com/apc). Estimates of the population size of PLHIV, and the number of patients initiating ART during 2005–2009 in Vietnam are presented in Supplementary Tables S2 and S3. The distribution of the number of patients initiating ART at various CD4 cell counts is estimated in Supplementary Table S4. The uncertainty ranges of transition probabilities were included in sensitivity analysis. Stratified utility weights for non-ART patients were obtained from the study by Tran et al.[27]

For ART patients, estimates for transition probabilities and mortality rates were cited from Tran et al.,[22] (Supplementary Table S5). Utility weights for ART patients in the corresponding CD4 categories were obtained from a Vietnamese study by Tran et al.[28,29] Health utilities among second-line ART patients were assumed to be identical to those in the corresponding CD4 category on first-line therapy.

Healthcare costs for patients who were on first-line and second-line therapy were obtained from a Ministry of Health report.[30] Personnel and management costs were assumed to be identical among patients across CD4 categories, but hospital admission, lab test, and opportunistic infection treatment costs were stratified according to CD4 cell count categories. Stratified costs were calculated by identifying the differences in the number of hospital admissions, the number of people who developed opportunistic infections, the frequency of acquired opportunistic infection, and the mean frequency of hospital admission within one year of initiating ART, in each CD4 category. Cost offset was not included in the study. Details of costs calculation are presented in Supplementary Tables S6–S11. All costs were reported in US dollars in 2010. A discount rate of 3% was used in the calculation both health benefits (QALYs) and healthcare cost.

Treatment scenarios

Three ART initiation thresholds (350 cells/mm^3, 500 cells/mm^3, and treat all patients) and various treatment commencement rates (from 5% to 100%) were investigated. Annual per person year ART cost, non-ART cost, total spending on first-line and second-line ART were calculated for each treatment scenario.

Cost-effectiveness analysis

The costs and outcomes of initiation treatment thresholds were estimated from the Vietnamese health care system perspective. Cycle length of observation was 1 year. The comparison time frame was 10 year follow up. Different ART initiation strategies were compared by examining improvements in health outcomes relative to service costs, quantified into QALYs. The ICER was also determined and compared across treatment scenarios.

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to examine the robustness of the results with the uncertainties of model parameters. Health utility and transition probabilities were assumed to follow triangular distributions, whereas costing data were uniformly distributed. Based on a Monte Carlo approach, 10,000 runs of the model were simulated with random selection of probability and utility values according to its distributions. Cost-effectiveness acceptability curves demonstrate the relationship between the likelihood of cost-effectiveness and society's willingness to pay (WTP) (three times GDPPC). The per-capita GDP in Vietnam is US $1,113.40 USD according to Vietnam's National General Statistics Office in 2010.[5,31]

Results

Demographics

The current study enrolled 3449 patients (75% males) during 2005–2009. A total 18,751 person-years were followed-up (median 1.38 years per person, interquartile range [IQR] 0.75–2.47). The mean age at baseline was 30 years old and the majority of the patients (73%) was infected through sharing of injecting equipment.[32]

Diagnosis and treatment

Average CD4 cell count at diagnosis significantly increased from 76 ± 68.6 cells/mm^3 in 2005 to 111 ± 114 cells/mm^3 in 2009 (ANOVA, F value = 17.77; $p < 0.001$). However, the overall ART commencement rates among diagnosed HIV patients remained low (Fig. 2), as only 19% of treatment-eligible patients (CD4 < 350 cells/mm^3) initiated ART within 12 months of diagnosis in 2009, a slight increase from 12% in 2006. Among patients in very late AIDS stages, more substantial increases were observed. ART commencement rates among patients in baseline CD4 categories < 50, 50–100, and 100–200 cells/mm^3 increased from 43%,19%, and 8% to 81%, 22%, and 8% during 2006–2009 (Fig. 2).

Projected impacts and cost-effectiveness of ART

The projected impacts and cost-effectiveness of ART are illustrated in Fig. 3 and Supplementary Table S12. In all threshold scenarios, increasing ART commencement rates required substantial scale-up of ART spending during 2010–2019. In particular, under the current treatment threshold, increasing commencement rates from the present 19% to 50% would require an extra investment of US $152 million for initiating ART in all eligible diagnosed patients. In scenarios where treatment thresholds were to scale up to 500 cells/mm^3 and 'treat all', the required investment on ART over 2009–2019 to maintain a 50% commencement rate

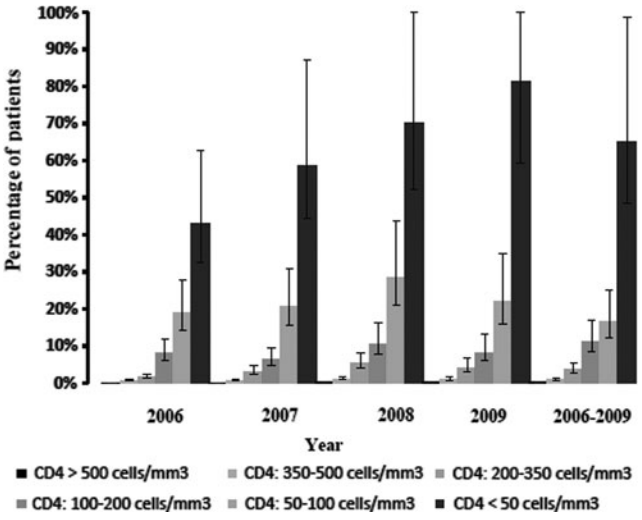

FIG. 2. Percentage of people living with HIV initiating ART within 12 months of HIV diagnosis.

would be US $805 and US $979 million, corresponding to extra US $300and US $474 million spending on ART from the government's perspective. However, per-capita annual ART cost at the current treatment threshold would decrease from the present US $880 (869–888) to US $871 (869–892) at 50% commencement rate and US $838 (831–888) at full commencement (Supplementary Table S12). Threshold scale-up to 500 cells/mm^3 and 'treat all' would reduce per-capita ART spending to US $838 (829–879) and US $817 (807–877) at the 50% commencement (Supplementary Table S12).

Expansion of ART would substantially add to the life quality of PLHIV in Vietnam. With the current treatment threshold, increasing treatment commencement from 19% to a moderate 50% would result in an extra 180,279 (142,515–228,884) person years (pyrs) on ART, which in turn averts 13,075 (8,912–22,068) HIV-related deaths during 2010–2019 and gains 125,741 (117,849–146,377) QALYs (Fig. 3b, 3c). These results in a very cost-effective US $381 (259–630) for each QALY gained. Further increases in treatment commencement would lead to a larger number of averted deaths, gained QALYS, and even lower cost for each QALY gained. At 50% treatment commencement, scale-up of treatment threshold to 500 cells/mm^3 and for all PLHIV would add extra 385,663 (342,070–436,728) and 623,155 (577,455–675,455) pyrs of treatment to the current PLHIV population in Vietnam (Supplementary Table S12). These would avert 17,973 (12,947–27,801) and 19,533 (13,524–30,320) HIV-related deaths and yield 164,464 (154,831–186,856) and 178,625 (166,136–203,842) QALYs, respectively (Fig. 3b, Supplementary Table S12). In these higher threshold scenarios, the required ART costs for each QALY gained are US $400 (293–606) and US $563 (462–742).

Increasing ART commencement rate is a more cost-effective strategy than upgrading the current treatment threshold for PLHIV in Vietnam. Supplementary Table S12 indicates that an extra US $71.8million investment on ART at the current treatment threshold over the period 2010–2019 would result in a gain of 213,261 (200,027–239,029) QALYs, the highest among the three treatment strategies. This also

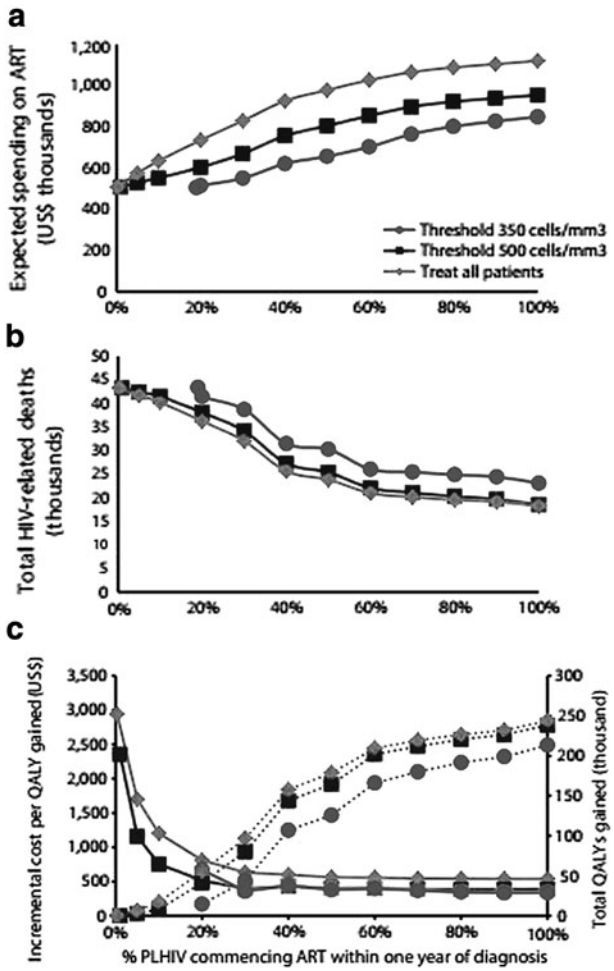

FIG. 3. Expected spending on ART, total HIV-related deaths, incremental cost per QALY gained in all ART expansion strategies.

represents the best value of money, as US $337 (227–522) would yield one extra QALY (Supplementary Table S12).

The optimal strategy in Vietnam would be to maintain the current ART initiation criterion, and to increase the rate of treatment commencement from the current 19% toward universal coverage. If the planned investment in HIV treatment in Vietnam over the next 10 years were increased to US $100 million, the CD4 cell count threshold for initiating ART could be upgraded: initiating ART at the threshold of 500 cells/mm^3 and treating all PLHIV in Vietnam (100% commencement) would result in an estimated US $816 (759.8–887.8) and US $6,846 (5,949–7,694) per QALY gained, respectively (Fig. 3c).

Sensitivity analysis

Sensitivity analysis was conducted based on 10,000 simulations in PSA. At the current treatment commencement rate, upgrading the current treatment threshold to 500 cells/mm^3 and 'treat all' were only cost-effective in 52.8%, and 54.6% of the times based on a cut-off of willingness-to-pay of three GDPPC per QALY gained. However, all scenarios are considered to be cost-effective when ART commencement rate is greater than 30% (Supplementary Fig. S1).

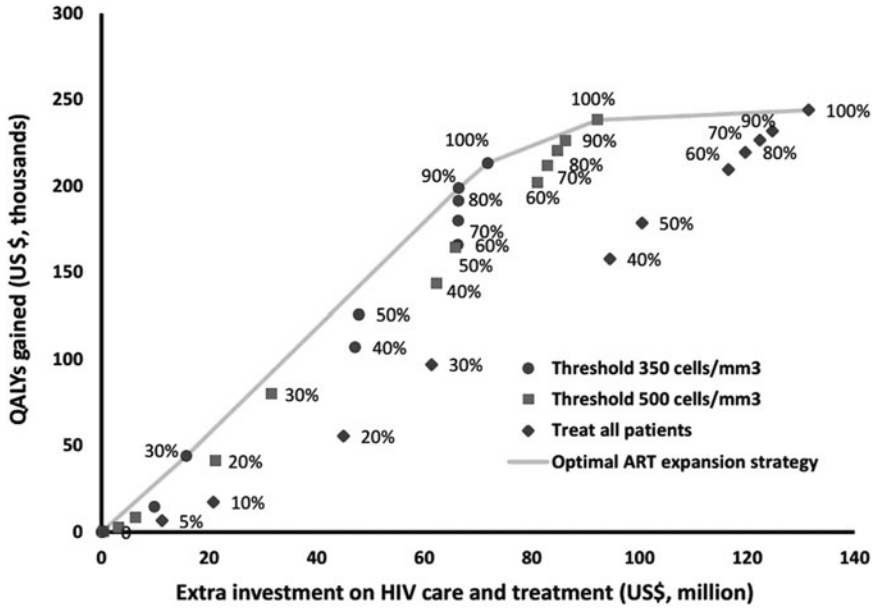

FIG. 4. Optimal ART expansion strategy in Vietnam between 2010 and 2019.

Discussion

Study outcomes and implications

This is the first Vietnamese study to combine actual patient data collected from a well-defined cohort with a robust analytical decision model, to provide context-relevant evidence. The results show that increasing access to ART and increasing the CD4 cell count threshold would both be cost-effective. This finding is consistent with previous studies from Vietnam.[12,17,33] More specifically, this study shows that the most cost-effective method of scaling-up ART in Vietnam would be to maintain the current ART treatment initiation threshold (CD4 cell count ≤ 350 cells/mm^3) but increase access from 19% to 30% of all eligible patients. The second most cost-effective method would be to maintain the current ART treatment initiation threshold but increase access to 90% of all eligible patients. The third most cost-effective method would be to increase the ART treatment initiation threshold to a CD4 cell count ≤ 500 cells/mm^3 and access to 100% of all eligible patients.

Achieving the most cost-effective method of scaling up ART treatment in Vietnam would require increasing the current rate of access to ART treatment from 19% to 30%. This study shows that the reason this would significantly improve the cost-effectiveness of ART treatment is that there would be fewer OIs and fewer laboratory tests (Supplementary Tables S6–S11). An additional benefit from treating more patients with higher CD4 cell counts is the reduced demand for more expensive second line ART in the first year after ART initiation. Increasing access from 19% to 30% is likely to be achievable, but it would require substantial effort to address the significant structural barriers to accessing HIV testing and treatment, including a lack of confidentiality, poor linkage between HIV care and ART clinics, and human resources shortages, as well as socio-cultural factors, such as punitive laws against drug users and female sex workers, along with the associated stigma and discrimination against PLHIV.[23]

The next two most cost-effective strategies are highly unlikely to be practical because the increased costs are prohibitive in a resource poor country like Vietnam. This study has estimated, for example, that it would cost $100 million to have ART initiation at 500 and 100% access (Fig. 4). Indeed, this cost estimate is likely to be an underestimate of the true cost because both these strategies would significantly increase demand for ART drugs, the cost of which is likely to become increasingly difficult to meet because external donor funds are reduced as Vietnam continues to transition from a low to middle-income country. If the government minimized the cost increase to them by passing on the increased cost to patients, this would be counterproductive in the sense that it would create a barrier to accessing treatment that would further undermine Vietnam's ability to achieve 100% access.

Strengths and potential limitations

This study has significant strengths. First, observational data reflecting the real-world situation in Vietnam were used, which provides high external validity. Second, patients' quality of life data were obtained from current Vietnamese HIV patients, and costing data were obtained from relevant Government reports, meaning data were collected using both a top-down and bottom-up approach. Third, the use of probabilistic sensitivity analyses, taking into account variations of transition probabilities, costs, and the utilities of the model, increases confidence in the validity of the statistical models.

The limitations of this study should also be noted. Since increasing model complexity does not necessarily provide more reliable results,[34] we simplified our model by combining all opportunistic infections rather than explicitly modeling all AIDS-defining diseases separately. Further, the transition probabilities are from 13 outpatient clinics, and cost data are from 11 clinics, so generalization of study findings should be made with caution, even though we did examine these model parameters in the sensitivity analyses and found that they did not have a major influence on the

outcomes. In addition, since our analyses assumed that patients entered the model using an identical ART pathway, but with different timing (i.e., earlier or later), we are unable to account for the possible variation in efficacies associated with different treatment pathways. The preventative effects of ART (i.e., that ART can reduce the number of people infected with HIV as well as treat those already infected) are not included in the model, which may underestimate its cost-effectiveness. These unmeasured preventative effects could be captured more effectively in an individual-based model that would strengthen its comprehensiveness.

Results from our studies showed that increasing threshold to 500 cells/mm^3 or treat all PLHIV regardless of CD4 cell counts at ART initiation are cost-effective. However, our model did not show how increasing CD4 threshold and HIV testing may influence treatment uptake and retention. This important question needs further work to address. Our findings may serve as an important evidence to support the decision making process for resources allocation and HIV health policies.

Finally, yet importantly, the model did not capture the factors that influence treatment uptake and real-life situation. The 19% of patients who have met the 350 threshold criteria and started ART within 12 months may be those who enrolled at the very beginning of the PEPFAR-funded ART expansion. We expect to expand this model, in future versions, to account for these variations.

Conclusions

Based on these findings, the most practical and cost-effective strategy Vietnam could implement to improve HIV treatment outcome would be to maintain the current CD4 cell count threshold and increase access to 30%. The main barrier for reaching this level is the poor access to targeted testing, the limited linkage between HIV care and ART clinics.[23] Our study, therefore, underscores the need to remove barriers to HIV testing, and ART accessibility to facilitate more timely recruitment of HIV patients into ART. Additionally, high risk groups (IDUs, sex workers, or males who have sex with males) should be encouraged to have routine, voluntary, and anonymous HIV testing, and PLHIV should be referred to ART clinics when they have been identified as meeting the eligibility criteria for ART initiation.

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Author contributions: DT collected data, reviewed literature, set up the model, and drafted the article. AS and AN provided guidance on data analysis as well as editorial comments and writing part of the article. JR set up the model, and provided technical advice on analysis. LZ provided guidance on data analysis, and commented on analysis. CD provided support to data collection, and editorial comments on the article. DW provided guidance on analysis. All authors have reviewed and agreed on the final version of the article prior to submission. The corresponding author has full access to all data in the study and takes final responsibility for the decision to submit the article for publication.

Author Disclosure Statement

No competing financial interests exist.

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