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Original Article

A systematic review and cost-effectiveness analyses of the new World Health Organization guidelines for the treatment of HIV-positive adults in India

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ARTICLE INFO

Article history:

Received 16 November 2017

Accepted 30 August 2018

Available online 22 November 2018

Keywords:

Health technology assessment

Human immunodeficiency virus

Antiretroviral therapy

Incremental cost-effective ratio

Quality-adjusted life years

ABSTRACT

Background: The World Health Organization (WHO) in 2013 has revised its guidelines on antiretroviral therapy (ART) treatment for human immunodeficiency virus (HIV)-positive adults and further updated it in 2016. Based on the WHO recommendations, in May 2017, National AIDS Control Organisation, India recommended initiation of ART treatment for all people living with HIV, regardless of CD4 count, clinical stage, age, or population. This systematic review aims to assess the clinical effectiveness and cost implication of the new guidelines for India.

Methods: A systematic and comprehensive literature search on PubMed, OvidSP, Cochrane Library, and Google Scholar was carried out. Studies reporting either acquired immunodeficiency syndrome (AIDS) or mortality or both as outcome variables were selected. A meta-analysis of the available studies was carried out. The risk ratio was calculated to assess the reduction in AIDS or mortality or both. Cost-effectiveness analysis using health technology principles evaluating the lives saved in terms of incremental cost-effectiveness ratio and cost per quality-adjusted life years gained was carried out.

Results: Nine eligible studies were included for the meta-analysis. For India, the pooled relative risk of AIDS or mortality or both being 0.84 (95% confidence interval [CI], 0.76–0.92) and 0.78 (95% CI, 0.68–0.89) for ART initiation at CD4 count of ≤ 350 vs CD4 count of ≤ 500

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<https://doi.org/10.1016/j.mjafi.2018.08.012>

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and at CD4 count of ≤ 500 vs CD4 count > 500 cells/mm³, respectively. The incremental cost for per additional life saved is US\$ 2592 and US\$ 2357 for ART initiation at ≤ 500 and > 500 CD4 count, respectively.

Conclusion: The adoption of the new WHO guidelines is beneficial with substantial reduction in AIDS or mortality or both. This study suggests that adopting new WHO guidelines is cost-effective for India.

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Introduction

Few decades ago, it was generally thought that infectious diseases were no longer a threat to the developed world. However, in the early 1980s, the world was hit with the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) epidemic. Today, the HIV epidemic is widely accepted to be a most severe health problem of modern times causing huge morbidity and mortality. In the last few years, the retroviral disease has changed from an incurable to a chronic disease because of the advances made in medical sciences and the understanding of the pathogenesis and treatment of HIV. Highly active antiretroviral therapy (ART) happens to be the backbone of treatment in HIV. However, the best time to introduce therapy still remains open.

The World Health Organization (WHO) in 2013 for the first time revised its guidelines and recommended ART initiation for HIV-positive adults with CD4 counts of 500 cells/mm³ or less,¹ as compared with the previously recommended 2010 guidelines threshold of 350 cells/mm³ or less.² These consolidated guidelines for the use of antiretroviral drugs for the treatment and prevention of HIV infection recommended ART for all HIV-positive adults whose CD4 count has fallen to 500 cells/mm³ or less, with treatment to be given irrespective of CD4 cell count for pregnant women, HIV-serodiscordant couples, and individuals with active tuberculosis or hepatitis-B-associated severe chronic liver disease. The main goals for initiating ART are to reduce HIV-associated morbidity through suppressing viral load and improving survival by restoring and preserving immunological function, thus preventing HIV transmission. Since 2013, strong evidence in the form of clinical trials and observational studies emerged in treatment of HIV patients which showed that using ART earlier results in better clinical outcomes compared with delayed treatment. Consequently, in June 2016, the WHO updated the guidelines and recommended ART initiation in all adults living with HIV, regardless of the WHO clinical stage and at any CD4 cell count.³

Based on the WHO recommendations, in May 2017, National AIDS Control Organisation (NACO) India recommended initiation of ART treatment for all people living with HIV, regardless of CD4 count, clinical stage, age, or population.⁴ For country like India with finite resources, how to maximize the preventive potential of ART still remains a challenge. The discussion on when to initiate therapy is ongoing especially in India as there is a lack of evidence on treatment initiation through observational studies as well as

randomized clinical trials. However, clinical trials as well as large observational studies are available in literature suggesting improvement in long-term outcomes by early initiation of ART.^{5–16}

The present systematic review aims at assessing the clinical as well as cost-effectiveness of changing the WHO guidelines on initiation of ART from time to time, that is, from 350 cells/mm³ to ≤ 500 cells/mm³ and then to CD4 count > 500 cells/mm³ for treatment of HIV-infected adults for India. We hypothesize that for India, the new WHO guidelines of ART initiation at CD4 count > 500 cells/mm³ will be clinically as well as cost-effective in reducing the risk of AIDS or mortality or both.

Materials and methods

The review is registered in the International Prospective Register of Systematic Reviews (PROSPERO, <http://www.crd.york.ac.uk/PROSPERO>: CRD42017069000).

Search strategy

We did a systematic and comprehensive literature search using an effective strategy in the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, PubMed, OvidSP, SCOPUS, and Google Scholar for relevant studies. Secondary referencing was also conducted by manually reviewing reference lists.

Selection of studies and data extraction

The studies included for meta-analysis assessed initiation of ART at CD4 count threshold with outcome as AIDS and/or mortality. Studies published in English language till 2017 were included for this review. The CD4 interval for ART initiation was chosen as less than 350, less than or equal to 500, and greater than 500. Studies which were available on this subject were compiled, and all duplicate studies were removed. The studies were independently screened for titles and abstracts to recognize appropriate papers. For all eligible studies, full-text articles were obtained. Studies were thoroughly assessed for variables which included study design, types of participants, exposures, and outcome measures. The data were extracted into a standardized data extraction form with the details of the author, year of publication, informed consent, ethical approval, and setting of the participants. CD4 count

and viral load was noted along with other baseline characteristics. The intervention details in terms of the CD4 count at which ART was initiated was documented. The outcomes in the form of progression to AIDS or mortality or both were extracted.

Primary outcome

Data analysis was conducted using Review Manager (Rev-Man), version 5.3. The data from the studies which were methodologically comparable were pooled for a meta-analysis. Meta-analysis comparing ART initiation at less than 350 and less than or equal to 500 was carried out. Using meta-analysis, a summary statistic relative risk with 95% confidence intervals (CIs) for dichotomous data, namely, AIDS or mortality or both were calculated for ART initiation at CD4 count ≤ 350 vs ≤ 500 and for ART initiation at CD4 count ≤ 500 vs > 500 . Subgroup analysis was carried out for observational studies and randomized trials separately. No sensitivity analysis was carried out.

Assessment of risk of bias in included studies

Publication bias was assessed using funnel plot. The components of each included trial were evaluated for risk of bias using a standard form. This included standard information on the sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The selected studies were then classified as having low risk, high risk, and uncertain as per the Cochrane Handbook of Systematic Reviews of Intervention and non-randomized trials.¹⁷

Assessment of heterogeneity

The hypothesis of the heterogeneity was assessed using the Cochran Q statistic, and I^2 test was used to measure the variation in study outcomes between studies.

Cost-effectiveness analysis

The cost-effectiveness was carried out for ART initiation at ≤ 500 and > 500 CD4 count. The cost and the effectiveness of initiating ART at different thresholds is compared in terms of the number of lives saved and the quality of life gained by adopting the WHO guidelines. The cost-effectiveness of a new therapeutic option is assessed by the incremental cost-effectiveness ratio (ICER). In this analysis, the effect in terms of reduction in progression to AIDS or death or both by starting ART at different CD4 threshold obtained by meta-analysis, and the additional number of people eligible for ART was obtained from the latest published reports. The cost-effectiveness ratio is calculated as the incremental cost per life saved and per quality-adjusted life year (QALY) gained. ICER is calculated for the pooled estimate of meta-analysis as well as for the worst scenario, that is, lower limit of 95% CI value of pooled estimate. The terms used and

assumptions made for cost-effectiveness analysis are as follows:

- i) Incidence of HIV and prevalence of HIV in India remains same in the near future.
- ii) **L** indicates the total number of people living with HIV in India and its value being taken as 1,978,125.¹⁸
- iii) **D** indicates the estimated number of annual AIDS-related deaths and its value being taken as 67,612.¹⁸
- iv) Mortality due to a cause other than related to HIV/AIDS is negligible.
- v) **P₁** indicates the percentage of HIV-positive people with CD4 count ≤ 350 and its value being taken as 73%.¹⁹
- vi) **P₂** indicates the percentage of HIV-positive people with CD4 count ≤ 500 and its value being taken as 85%¹⁹ and thus percentage of HIV-positive people with CD4 count > 500 (**P₃**) is to be 15%.
- vii) **P** indicates the additional burden to government for ART treatment:
 - a. For initiation of ART at CD4 count of ≤ 500 cells/mm³ = **P₂** - **P₁** = 237,375.
 - b. For initiation of ART at CD4 count of > 500 cells/mm³ = **P₃** = 296,719.
- viii) **C** indicates the cost for ART treatment per patient per year under National AIDS Control Programme (NACP), India, and its value being taken as US\$133.89²⁰ (Rs 8032/-).
- ix) Reduction (Δr) in AIDS or mortality or both due to initiation of ART at CD4 count more than 500 cells/mm³ and using meta-analysis, it is estimated to be one minus relative risk (**1-RR**).
- x) Total number of lives saved or averted AIDS (Δm) due to initiation of ART at CD4 count more than 500 cells/mm³ ($\Delta m = D * \Delta r$).
- xi) ΔC indicates the additional cost incurred due to policy change of ART initiation at CD4 count more than 500 cells/mm³ ($\Delta C = C * P$).
- xii) ΔQ indicates the additional QALY gained per person per year due to initiation of ART at varying CD4 threshold as per the changing WHO guidelines.
- xiii) **ICER** indicates the ICER, and it is defined as the ratio of ΔC to Δm , that is, $\Delta C / \Delta m$.
- xiv) Cost per additional QALY gained is defined as the ratio of ΔC to ΔQ , that is, $\Delta C / \Delta Q$.

Results

Meta-analysis

The initial literature search by two authors resulted in 1419 studies; of which, nine studies were found to be eligible for meta-analysis after excluding studies which were irrelevant, duplicate, multiple overlapping subcohorts, and different outcomes (Fig. 1). Of the nine studies, seven were observational, and two studies were randomized controlled trial (RCT) studies. All studies included for meta-analysis were with large sample size and conducted across Europe, United States, Africa, Australia, Canada, Barcelona, Japan, and France. The seven observational cohort studies had the outcome as AIDS

or mortality or both, and one of these had an additional outcome of AIDS-defining illnesses and another had serious non-AIDS-defining diseases. Of two RCTs, one had composite end point of death from any cause, AIDS-defining disease, non-AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease; and the other RCT had serious AIDS and non-AIDS-related event. Table 1 shows the characteristics of these selected studies. These studies had varying reference categories with respect to CD4 count; however, data were extracted for the three categories of interest namely, CD4

count ≤ 350 cells/mm³, CD4 count ≤ 500 cells/mm³, and CD4 count > 500 cells/mm³.

Comparison of an event of AIDS or death or both between initiation of ART at CD4 count ≤ 350 vs CD4 count at ≤ 500 cells/mm³

Seven observational studies were identified which compared initiation of ART at CD4 count of ≤ 350 vs ≤ 500 cells/mm³. In

Fig. 1 – Study flow diagram.

Table 1 – Characteristics of the studies.

Study no., author	Study year	Location	Study population (n)	Follow-up in months	Reference CD4 categories	Outcomes
Cain ⁸	2011	Europe and US	20,971	N/A	350–499	AIDS and/or death
Funk ⁹	2011	Europe, Australia, and Canada	9455	56.4	<350	AIDS and/or death
Garcia ¹⁰	2004	Barcelona	861	8	≥500	CD4 T-cell recovery, AIDS and/or death
Kawado ¹¹	2003	Japan	605	60	≥500	AIDS or death
Lifson ¹²	2012	US (military personnel)	1600	104.4	>500	Death
Lelyveld ¹³	2012	Netherlands	3068	24	>500	AIDS and severe non-AIDS-defining diseases
Lodi ¹⁴	2015	Europe and the USA	55,826	84	>500	AIDS event or death
START ¹⁵	2015	Open trial	4685	36	<500	Serious AIDS-related event
TEMPRANO ¹⁶	2015	Africa, Abidjan, the economic capital of Ivory Coast.	2076	30	<500	Composite of death from any cause

AIDS, acquired immunodeficiency syndrome.

these studies, the RR, that is, risk of occurrence of AIDS or mortality or both among HIV patients on ART ranged from 0.44 to 0.96. Thus, these studies reported decreased risk of AIDS or mortality or both and by meta-analysis, the pooled estimate of RR was 0.84 (95% CI: 0.79 to 0.89) which was statistically significant ($p = 0.000$) (Fig. 2). Thus, there was a reduction of 16% in AIDS or mortality or both by initiating ART at CD4 count of ≤ 500 cells/mm³. The I^2 statistic value is 30% that indicates that there is a sufficient homogeneity in the included studies.

Comparison of an event of AIDS or death or both between initiation of ART at CD4 count ≤ 500 vs CD4 count at > 500 cells/mm³

Nine studies were identified which compared initiation of ART at CD4 count at ≤ 500 vs. > 500 cells/mm³. Of these nine studies, seven were observational studies and two were RCTs. In these studies, RR ranged from 0.44 to 0.91, and five

studies showed significant difference while four studies showed no significant difference between CD4 count at ≤ 500 vs. > 500 cells/mm³. The pooled estimate of RR by meta-analysis was 0.78 (95% CI: 0.68–0.89) which was statistically significant ($p = 0.000$) (Fig. 3). Thus, there was a reduction of 22% in AIDS or mortality or both due to initiation of ART at CD4 count > 500 as compared with ≤ 500 cells/mm³, thus favoring the new WHO guideline of initiation of ART irrespective of CD4 count. I^2 statistic value was 58%, indicating that there is a sufficient heterogeneity among studies included.

Further data were analyzed by taking account of type of study, that is, data analyzed separately for observational studies and RCTs (Fig. 4). The pooled estimate of RR by meta-analysis for observational studies and RCTs was 0.87 (95% CI: 0.81–0.92) and 0.55 (95% CI: 0.31–0.96), respectively. RR in observational studies varied in the range of 0.75–0.91, and of seven studies only three showed significant reduction in outcome of interest while RR in RCTs varied in the range of 0.44–0.81, and of the 2 studies, one showed

Fig. 2 – Forest plot for AIDS and/or mortality comparing ≤ 350 vs ≤ 500 threshold of CD4 count for ART initiation. AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval.

Fig. 3 – Forest plot for AIDS and/or mortality comparing ≤ 500 vs > 500 threshold of CD4 count for ART initiation. AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CI, confidence interval.

significant reduction in outcome of interest. The reduction in outcome of interest in RCTs is much more than observational studies.

Cost-effectiveness analysis

Cost-effectiveness analysis was carried out for the two outcomes, namely, the number of lives saved or averted AIDS and the quality of life gained under the assumptions mentioned in the Materials and methods section. The cost-effectiveness analysis was performed for two situations; one for pooled

estimate and another for its lower limit of 95% CI as a worst scenario for ART initiation at CD4 count ≤ 350 vs ≤ 500 , ART initiation at CD4 count ≤ 500 vs > 500 (observational + RCTs), ART initiation at CD4 count ≤ 500 vs > 500 (observational studies), and ART initiation at CD4 count ≤ 500 vs > 500 (RCTs) (Table 2). ART initiation at ≤ 500 as compared to ART initiation at CD4 count ≤ 350 reduces the risk of AIDS or mortality or both by 16% (worst scenario: 8%) with incremental cost of US\$ 2592 (worst scenario: US\$ 5185) per additional life saved. Similarly, for ART initiation at more than 500 as compared to ART initiation at CD4 count ≤ 500 (observational + RCTs)

Observational Studies

RCTs

Fig. 4 – Subgroup analysis. CI, confidence interval

reduces the risk of AIDS or mortality or both by 22% (worst scenario: 11%) with incremental cost of US\$ 2357 (worst scenario: US\$ 4713) per additional life saved, for ART initiation at >500 as compared to ART initiation at CD4 count $\leq$ 500 (observational) reduces the risk of AIDS or mortality or both by 13% (worst scenario: 8%) with incremental cost of US\$ 3988 (worst scenario: US\$ 6481) per additional life saved and for ART initiation at >500 as compared to ART initiation at CD4 count $\leq$ 500 (RCTs) reduces the risk of AIDS or mortality or both by 45% (worst scenario: 4%) with incremental cost of US\$ 1152 (worst scenario: US\$ 12,962) per additional life saved.

The health-related quality of life considered from published literature²¹ is shown in Table 3. There is no considerable gain in health-related quality of life years gained (QALY) with respect to CD4 count at ART initiation $\leq$ 500 cells/mm³, however, there is a marginal gain in QALY by 0.01 when ART is initiated at 500 or more CD4 count.

The risk of bias brings out that overall the studies show a low risk of any form of bias implying that the findings of respective studies were of high scientific validity and reliability (Fig. 5).

Discussion

Policymakers and clinicians aiming at most effective and efficient treatment modalities to HIV patients are affected by the change in the HIV therapy initiation guidelines.⁵ In May 2017, NACO⁴ made a policy change and recommended initiation of ART treatment for all people living with HIV, regardless of CD4 count, clinical stage, age, or population. However, the health policy-related decisions need to be evaluated from time to time, and this article is an attempt in that direction. In such a scenario, we may have to resort to assessing our decisions to see if the policy requires any amendment. To the best of our knowledge, this is the first article assessing the clinical effectiveness as well as the cost implication of the changing WHO guidelines for India although there exist scant literature on the cost-effectiveness based on small cohorts and simulated models. We could identify nine studies of which seven were observational studies and 2 landmark RCTs

Table 3 – Health-related quality of life.

S. No	CD4 cell count, cells/mm ³	Quality adjustment
1	>500	0.87
2	301–500	0.86
3	201–300	0.86
4	101–200	0.85
5	51–100	0.85
6	0–50	0.83

Adopted from the study by Kimmel et al.²¹

namely the Strategic Timing of AntiRetroviral Treatment (START) trial¹⁵ and Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (ANRS 12136 (TEMPRANO) ANRS trial.¹⁶ All these studies investigated association between CD4 cell count at ART initiation and reduction in the risk of AIDS and/or mortality. These studies had CD4 count categories of our interest and hence were included for the meta-analysis. Of these studies, Cain et al,⁸ Funk et al,⁹ García et al,¹⁰ Kaplan et al,¹¹ and Lifson et al¹² had same CD4 categories. The study by Van Lelyveld¹³ had CD4 categories of 200–350, 351–500, and >500. Two studies^{6,7} had comparison in the early and deferred treatment within the same subgroup as well as with multiple overlapping subcohorts and hence were not included. Also, although HPTN 052²² clinical trial strongly recommended early initiation of ART and included patients from Asia, it was not included for meta-analysis as comparable CD4 class interval of interest was not present. Including studies with varying CD4 count would have increased the heterogeneity and hence were excluded from meta-analysis.

In resource constraint countries, initiation of ART at the new WHO threshold may not be adhered to or meet resistance as it is a financial burden. Our review gives the insights into the risk and the costs associated by adopting these thresholds. The pooled data from meta-analysis suggested that ART initiation irrespective of CD4 count reduces the risk of AIDS and/or mortality. However, with coverage of ART around 42%, a sizable proportion of deaths are of those who are on ART and have failed. Hence, the current calculations overestimate lives saved which impacts ICER. Our review suggests that adoption

Table 2 – Cost-effectiveness analysis.

	RR	L	D	Δr	Δm	P	ΔC	ICER	
								Rs	US\$
ART initiation at CD4 count ≤350 vs ≤ 500									
Pooled estimate	0.84	1,978,125	67,612	0.16	10,818	237,375	1,906,596,000	176,243	2592
Worst scenario	0.92	1,978,125	67,612	0.08	5409	237,375	1,906,596,000	352,488	5185
ART initiation at CD4 count ≤500 vs > 500, for observational + RCTs									
Pooled estimate	0.78	1,978,125	67,612	0.22	14,875	296,719	2,383,245,000	160,222	2357
Worst scenario	0.89	1,978,125	67,612	0.11	7437	296,719	2,383,245,000	320,444	4713
ART initiation at CD4 count ≤500 vs > 500, for observational studies									
Pooled estimate	0.87	1,978,125	67,612	0.13	8790	296,719	2,383,245,000	271,145	3988
Worst scenario	0.92	1,978,125	67,612	0.08	5409	296,719	2,383,245,000	440,611	6481
ART initiation at CD4 count ≤500 vs > 500, for RCTs									
Pooled estimate	0.55	1,978,125	67,612	0.45	30,425	296,719	2,383,245,000	78,331	1152
Worst scenario	0.96	1,978,125	67,612	0.04	2704	296,719	2,383,245,000	881,221	12,962
ART, antiretroviral therapy; ICER, incremental cost-effectiveness ratio; RCT, randomized controlled trial; RR, relative risk.									

ART, antiretroviral therapy; ICER, incremental cost-effectiveness ratio; RCT, randomized controlled trial; RR, relative risk.

Fig. 5 – Risk of bias analysis for comparing various threshold of ART initiation as per WHO guidelines. ART, antiretroviral therapy; CI, confidence interval; WHO, World Health Organization.

of the new guidelines for ART initiation irrespective of CD4 count will cost India from 1152 US\$ to 3988 US\$ per live saved.

The studies were subjected to thorough quality assessment tools and the risk of bias for each study was carried out as per Cochrane Handbook of Systematic Reviews of Intervention and non-randomized trials which revealed an overall low risk of bias. The quality of the observational literature was low because of its observational status and the lack of strength as of seven studies four studies showed non-significant difference. The funnel plot brings out no publication bias.

A previous systematic review and meta-analysis⁵ was the only one providing an evidence on optimal ART initiation threshold by comparing ART treatment at >500 cells/mm³ and

between 350 cells/mm³ and 500 cells/mm³. The study estimated 11% increase in risk for ART treatment at 350–500 cells/mm³. However, the review did not carry any cost-effectiveness analysis. Another study by Eaton JW²³ showed through mathematical modeling the cost-effectiveness of adopting new WHO guidelines for India. As per this study in India, the cost for extending ART treatment at CD4 counts of 500 cells/mm³ or less ranged from \$131 to \$241 per DALY averted. The study further stated that in concentrated epidemics as in India, improving access to the treatment for key populations was also cost-effective. In various studies of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)^{24–27} international model, the researchers simulated HIV disease,

treatment, and transmission comparing early ART with delayed ART. According to the findings of the CEPAC the guidelines of increased CD4 threshold to less than 500 decreased the incidence of AIDS to 12%. According to the cost-effectiveness study by HPTN 052,²⁸ the authors concluded that in India, early ART at CD4 count of 500 or less is cost-effective (\$1800 per life-year saved) and very cost-effective (\$530 per life-year saved) over a 5-year period and over lifetime, respectively.

The article assumes that progression to AIDS and death are equal. However, once a patient develops AIDS, the average survival without any intervention is about 18 months. India continues to rely on immunologic monitoring while providing ART. However, once we initiate ART earlier, one would require virologic monitoring. It is not included in ICER. Second, adoption of the new WHO recommendations in India would also mean that a large number of Persons living with (PLW) HIV would become eligible for ART which would put NACP at an increased financial burden. Adding 15% of additional patients in the system may also require additional human resources to handle these patients. Hence, while adopting the new guidelines careful planning needs to be carried out for costs, human resources to infrastructure, drug requirements, and the logistics.¹⁹ Political will and governmental support and increase in funding is required to scale up ART programs to accommodate the increased demand in India.

The findings from our study provide evidence of the reduction in AIDS/mortality risk by adopting the new guidelines and needs to be viewed in connection with the problem of low detection rate, loss to follow-up, and low adherence. Although India has made a remarkable progress in containing its HIV epidemic by National AIDS Control Programme, the detection rate for HIV remains low. As per the latest NACO report, 28% approximately half a million of infected people in India have not been diagnosed and are not aware of their HIV status. Thus, early detection and timely treatment is still a challenge for India. Second, although ART treatment has been rapidly scaled up in India, most HIV-positive patients present with late stage and low CD4 count to the ART center. Studies^{29–31} have recorded median CD4 count at the time of HIV diagnosis as low as 119 cell/mm³ and around 71% of HIV-positive report with less than 200 cells/mm³. A study in Karnataka state reported only 15% proportion of HIV-positive people with CD4 count of greater than 500 cells/mm³ and 85% below 500 CD4 count were registered. Thus, the additional burden for India with the new WHO and NACO guidelines is around 15%.

Further loss to follow-up and low adherence remains the major challenge in the success of ART treatment.³² Lost to follow-up patients develop drug resistance virus resulting in failure to treatment and increasing the risk of death because of AIDS.³³ One needs to do thorough investigation into the reasons of loss to follow-up and discontinuation of ART treatment. While antiretroviral treatment is free in India since 2004, uptake remains low. Moreover, as per the United Nations Programme on HIV and AIDS (UNAIDS), barriers like stigma prevent patients from accessing vital health-care services in India. Hence, intense scaling up of ART program is required at the time of adopting the new guidelines. The grave problem of adherence which is critical for long-term

outcomes in HIV-infected patients needs to be addressed, and support services to nonadherent patients are necessary to meet their needs.^{34–36}

In the prevailing uncertainties about acceptance of the revised WHO recommendations by many countries, this assessment paper tried to evaluate the current evidence available from epidemiological and biological information for the optimal time to initiate ART in HIV-infected adults. Assessing the observational studies reveals that there is evidence of moderate to high quality suggesting reduction in mortality rates by increasing the ART initiation threshold. Among the two trials, the START trial¹⁵ shows clear benefit in favor of higher threshold as compared with the TEMPRANO trial.¹⁶

We need to acknowledge certain limitations of our study. The meta-analysis included large observational and clinical trials with variable sample sizes as well as variable follow-up time; however, to reach objectivity, studies which were methodologically sound enough were included in this meta-analysis. Another limitation of the study is that sensitivity analysis was not carried out. We did not include the HPTN 052 study which actually paved way toward early initiation of ART as comparable CD4 class interval of interest to our analysis was not available. NACO implemented the new policy of ART initiation irrespective of CD4 count in India in 2017; however, inadequate data exist to show the beneficial effect of policy change. However, with time, it is expected that mortality and AIDS events will reduce in India.

Based on our assessment, we anticipate that if the developing countries adopt the new WHO guidelines there can be reduction in incidence of HIV infection and also countries health finances. This paper provides supportive evidence in adopting the new guidelines for India.

Conflicts of interest

The authors have none to declare.

Acknowledgments

The authors are thankful to Dr Akriti Chahar and Dr Prakash S Shah for their assistance.

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