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Cost-effectiveness analysis of 'test and treat' policy for antiretroviral therapy among heterosexual HIV population in India

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***Background & objectives*: The World Health Organisation recommended immediate initiation of antiretroviral therapy (ART) in all adult human immunodeficiency virus (HIV) patients regardless of their CD4 cell count. This study was undertaken to ascertain the cost-effectiveness of implementation of these guidelines in India.**

***Methods*: A Markov model was developed to assess the lifetime costs and health outcomes of three scenarios for initiation of ART treatment at varying CD4 cell count <350/mm^3, <500/mm^3 and test and treat using health system perspective using life-time horizon. A few input parameters for this model namely, transition probabilities from one stage to another stage of HIV and incidence rates of TB were calculated from the data of Centre of Excellence for HIV treatment and care, Chandigarh; whereas, other parameters were obtained from the published literature. Total HIV-related deaths averted, HIV infections averted and incremental cost-effectiveness ratio per quality adjusted life years (QALYs) gained were calculated.**

***Result*: Test and treat intervention slowed down the progression of disease and averted 18,386 HIV-related deaths, over lifetime horizon. It also averted 16,105 new HIV infections and saved 343,172 QALYs as compared to the strategy of starting ART at CD4 cell count of 500/mm^3. Incremental cost per QALY gained for the immediate initiation of ART as compared to ART at CD4 cell count of 500/mm^3 and 350/mm^3 was ₹ 46,599 and 80,050, respectively at reported rates of adherence to the therapy.**

***Interpretation & conclusions*: Immediate ART (test and treat) is highly cost-effective strategy over the past criteria of delayed therapy in India. Cost-effectiveness of this policy is largely because of reduction in the transmission of HIV.**

Key words Antiretroviral therapy - CD4 - cost-effectiveness analyses - economic evaluation - HIV - India – modelling - test and treat

Antiretroviral therapy (ART) to human immunodeficiency virus (HIV) patients in India is provided free of cost through a network of 319 care and support centres, 579 ART centres, 1261 link ART centres, 85 ART plus centres and 18 centres of excellence (CoE)[1]. However, despite this the coverage

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of ART treatment remains low at 43 per cent[1]. On the contrary, India is committed to end AIDS epidemic as a public health threat by 2030, a goal which aspires 90-90-90 targets aimed at diagnosing 90 per cent of total people living with HIV (PLHIV), putting 90 per cent of them on active ART and achieving viral suppression in at least 90 per cent of those on ART[1]. In order to achieve this, the National AIDS Control Organisation (NACO) has revised its ART policy as per the World Health Organisation (WHO) guidelines, to initiate ART treatment immediately upon diagnosis (test and treat)[1,2].

Any shift in the treatment guidelines such as test and treat implies large scale-up of ART services. A previous analysis of implication of changing the cut-off of initiation of ART treatment from 350/mm^3 CD4 cell count to 500/mm^3 reported that number of eligible patients will increase from 0.92 to 1.17 million[3]. However, no assessment of economic implications associated with change in ART guidelines was undertaken. With the setting up of Health Technology Assessment in India (HTAIn) in India, there is an increasing emphasis on justifying new interventions based on their value for money through cost-effectiveness analyses[4,5]. Moreover, National Strategic Plan for HIV/AIDS and sexually transmitted infections (STI) 2017-2024' of NACO specifically enlist the identification of cost-effective approaches through stochastic modelling of interventions among the areas of priority for evidence generation[6]. Furthermore, other countries have evaluated cost-effectiveness of test and treat in their settings[7-9] for evidence-based decision-making and rationale resource allocation. It hence, becomes important to ascertain cost-effectiveness of this intervention in the Indian context also, for best outcomes with given funding.

In terms of evidence on cost-effectiveness of ART therapy, two Indian studies are available[10,11]. Maddali *et al*[11] reported that early initiation (CD4 <500/mm^3) is cost-effective as compared to late initiation (CD4 <350/mm^3). However, it does not specifically include the test and treat as a scenario. While Eaton *et al*[10] assessed the cost-effectiveness of introduction of test and treat in four countries including India; most of the parameters on the valuation of cost and consequences were regional and not India specific. Second, the clinical evidence was derived from men having sex with men (MSM) population and considered an idealistic scenario which did not factor in the lack of adherence in the real-world scenario.

Hence, this analysis was undertaken to evaluate the cost-effectiveness of the fairly recent NACO intervention, *i.e*. immediate initiation of ART (test and treat policy), through estimation of the cost per quality-adjusted life-year (QALY) gained.

Material & Methods

Model overview: A probabilistic Markov model (Fig. 1) was used to simulate the disease progression and estimate the costs and consequences. Scenario I composed of 'test and treat'. The two comparators included ART initiation at CD4 count <500/mm^3 (Scenario II) and CD4 count <350/mm^3 (Scenario III), respectively (Fig. 1). All costs were calculated from health systems perspective because ART is delivered to all HIV patients for free through the public healthcare system[2]. The analysis was undertaken using the annual cycles and a life time horizon of HIV patients, *i.e*. we modelled the costs and health outcomes of the cohort were modelled till the average life expectancy of the cohort was reached. All future costs and consequences were discounted at three per cent annual rate to adjust for the time difference between money spent and benefits gained. The probability of acquiring opportunistic infections (OI) such as herpes, other viral infections, tuberculosis and candidiasis was also incorporated according to their CD4 cell count. Second, the development of malignancies such as non-Hodgkin's lymphoma, Kaposi's sarcoma and head-and-neck cancers was also modelled for all scenarios. Third, the development of adverse drug reactions such as hepatitis, lipodystrophy, anaemia, skin reactions, gastric disturbances and immune reconstitution inflammatory syndrome, *etc*. as a result of ART administration was also incorporated into this model.

Taking 2017 as a base year, all adult PLHIV registered with NACO (1,141,531) entered the model and were assigned to different stages according to their CD4 cell count[12]. Each of the three scenarios differed in terms of ART initiation. In all three scenarios, the disease followed its natural course and patients were under continuous care through counselling, testing of CD4 levels and prophylaxis/treatment for OIs. Finally, incremental cost per QALY gained was computed from 'test and treat' (Scenario I) as compared to Scenario II and III, respectively. In addition, incremental cost per QALY gained was also estimated for Scenario II as compared to Scenario III as depicted in the Supplementary Figure 1.

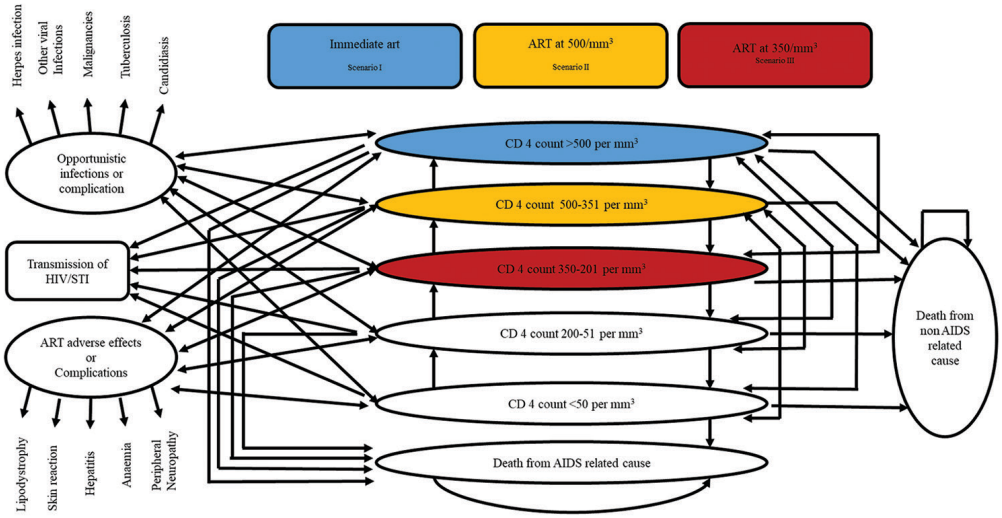

Fig 1. Markov state model. ART, antiretroviral therapy; STI, sexually transmitted infections.

Transition probabilities from one stage of HIV to another were calculated using the primary longitudinal follow up data obtained from a CoE situated in a large tertiary care hospital in North India. A cohort analysis was done after extracting information comprising of 1115 life-years follow up data of HIV patients registered with CoE. This included patients on ART as well as those on pre-ART care. The mix of patients included patients with the reported levels of adherence to the therapy along with those on the second or third line of ART drugs making results more realistic as compared to an RCT. The annual rate of transition from one stage to another was calculated, which was then used to compute annual transition probabilities which are summarized in Tables I and II. Detailed methodology used to derive these probabilities is provided Supplementary Material. These transition probabilities hence derived were then used as input parameters in our mathematical model for the estimation of health outcomes in all three different scenarios.

HIV stage wise health-related quality of life data, *i.e*. health state utility values corresponding to our model transition states are not available from India. Hence, these data were used from a study of health-related states of HIV patients reported for the United States[13]. We also modelled the risk of subsequent transmission of HIV by PLHIV through the heterosexual route for each of the different scenarios using Weinstein's equation[14]. By means of Weinstein's equation, we incorporated the effect of various behavioural factors such as number of sex partners, frequency of sex acts per partner and condom use along with other factors such as probability of transmission through different routes, prevalence of HIV and STDs in the general population and efficacy of condom in the prevention of HIV transmission. The input parameters for Weinstein equation were obtained from the national level behavioural sentinel surveys in India and other published literature[7]. Major model input parameters used in the analysis along with sources are given in Table III.

Costing: Overall, the cost in each scenario comprised of the cost of ART treatment, pre-ART care, and treatment of OIs and management of adverse drug effects due to ART. The difference in cost between different scenarios is typically attributable to the differences in the number of eligible patients on pre-ART and ART treatment and the duration of treatment due to differences in longevity[3]. The difference in the number of HIV patients requiring pre-ART and ART care was a result of change in criteria for the initiation of treatment and the number of new HIV transmissions. Differences in longevity are attributable to improved survival with early initiation of ART. Cost of delivery (COD) of ART as reported from a recent study which used the bottom-up costing approach to ascertain the annual cost at different levels of service delivery, *i.e.* CoE and ART centre, was used[15]. This analysis also incorporated cost of delivering ART to patients on second as well as third line therapy, which make the results of this analysis more realistic. Cost of treatment of OIs was taken from published literature. Cost of treatment of herpes infection, other viral infections and candidiasis was taken from an analysis done in 14 public sector STI clinics in the State of Andhra Pradesh[16]. Cost of treatment of tuberculosis was obtained from the study

Table I. One year transition probabilities according to CD4 count of HIV patients on antiretroviral therapy treatment

Transition from	Transition to						
	>500	500-351	350-201	200-51	<50	Death	Total
>500	0.870368	0.103504	0.018913	0.003558	0.000258	0.0034	1
500-351	0.607733	0.25524	0.103966	0.019466	0.002831	0.010764	1
350-201	0.360626	0.309714	0.26786	0.039035	0.004243	0.018523	1
200-51	0.224178	0.18636	0.277077	0.286736	0.008414	0.017236	1
<50	0.123626	0.079732	0.194485	0.244758	0.117818	0.23958	1

Table II. One year transition probabilities according to CD4 count of patients not on antiretroviral therapy treatment

Transition from	Transition to						
	>500	500-351	350-201	200-51	<50	Death	Total
>500	0.788259	0.157966	0.023071	0.013014	0.000728	0.016961	1
500-351	0.456170	0.465240	0.035449	0.018120	0.001080	0.023941	1
350-201	0.194646	0.105706	0.461459	0.098165	0.007117	0.132907	1
200-51	0.218150	0.005178	0.013052	0.344832	0.119707	0.299082	1
<50	0.157412	0.008889	0.161666	0.008889	0.323366	0.339778	1

done in Tamil Nadu State covering all public health facilities in one district[17]. This cost included capital costs such as infrastructure, furniture, equipment, instruments, *etc*. and various recurrent costs such as HR cost, cost of drug regimen, sputum examination cost, cost of chest X-rays done and cost of monitoring/supervision, *etc*. Cost of management of malignancies was derived from an economic costing done in a large tertiary care hospital in north India[18]. This analysis included the capital as well as recurrent costs pertaining to service delivery including staff salaries, equipment, space rent and consumable, *etc*. Cost of management of adverse drug reactions or complications due to ART was used as reported from the analysis of data from a Chennai-based treatment and research institute covering about 16 cities of India[19]. All costs were adjusted to 2018 using year specific inflation rates for India based on consumer price index.

Sensitivity analysis: Univariate analysis was done by varying various input parameters pertaining to cost, health utility states, demography and epidemiology from their lower to upper value to ascertain their effect on overall incremental cost-effectiveness ratio (ICER) of the intervention. The results were sorted according to their impact on ICER and a tornado chart was formulated to present the effect of the most impactful input parameters on ICER of Scenario I *vs*. Scenario II.

Probabilistic sensitivity analysis (PSA) was also performed using MS Excel and Visual Basic (Microsoft Office 2013) to compare the effect of joint variation of all the inputs parameters on ICER. We performed 1000 simulations to ascertain the variability in ICER using the different random values for selected input parameters using beta, gamma and log-normal distribution. The results were plotted in cost-effectiveness acceptability curve and cost-effectiveness plane.

Results

Costs: Implementing test and treat in India at the national level will impose extra cost to the healthcare system due to increased number of eligible patients and overall longevity of treatment. This cost was ascertained by this study to be ₹ 348542.30 million during lifetime horizon in test and treat, in comparison to ₹ 326272.30 million in Scenario II and ₹ 274694.10 million in Scenario III, as summarised in Table IV and Supplementary Table V. Major proportion from the total expenditure made by the healthcare system on treatment and care of PLHIVs was of cost of ART delivery which constituted about 90-95 per cent of the total cost, whereas only 5-10 per cent was the share of

Table III. Various input parameters used in the simulation models and their sources

Parameter	Value	Lower limit	Upper limit	Source reference
Demographic and epidemiological parameters				
Adults in active care at ART centres	1,141,531	856,148	1,426,913	1
Average age of HIV patient at the time of diagnosis (yr)	35.55	35.55	35.55	Primary data
Stages of patients on the time of diagnosis of HIV (proportion)				
CD4 >500	0.0639	0.051	0.166	12
CD4 500-351	0.0694	0.055	0.832	12
CD4 350-201	0.2167	0.173	0.260	12
CD4 200-51	0.1833	0.365	0.375	12
CD4 <50	0.4667	0.373	0.560	12
Adherence rate to ART (%)	75.50	41	97	24
Transmission per 1000 PYs through heterosexual route				
On ART	5.9700	5.9700	5.9700	14
Not on ART	29.8178	29.8178	29.8178	14
Proportion of patients taking treatment in CoE	4	4	4	15
Proportion of patients taking treatment in ART centre	96	96	96	15
Incidence of opportunistic infections or complications (ART)				
Herpes infection	0.04208861	0.02273752	0.07688365	21
Other viral infections	0.044958038	0.01783897	0.10684934	21
Malignancies	0.004987521	0.0029955	0.00796809	21
Candidiasis	0.048770575	0.03149342	0.07411015	21
Incidence of TB at CD4 >500	0.0180505	0.01444	0.021661	Primary data
Incidence of TB at CD4 500-351	0.0330579	0.026446	0.039669	Primary data
Incidence of TB at CD4 350-201	0.0391304	0.031304	0.046956	Primary data
Incidence of TB at CD4 200-51	0.0616438	0.049315	0.073973	Primary data
Incidence of TB at CD4 <50	0.4	0.32	0.48	Primary data
Incidence of opportunistic infections or complications (pre-ART)				
Herpes infection	0.089717238	0.0648048	0.123659	21
Other viral infections	0.058235466	0.02663876	0.12014662	21
Malignancies	0.011928287	0.00598204	0.02273752	21
Candidiasis	0.173867412	0.12190457	0.23890721	21
Incidence of TB at CD4 >500	0.0273493	0.0273493	0.0273493	Primary data
Incidence of TB at CD4 500-351	0.0500877	0.0500877	0.0500877	Primary data
Incidence of TB at CD4 350-201	0.0592885	0.0592885	0.0592885	Primary data
Incidence of TB at CD4 200-51	0.0933998	0.0933998	0.0933998	Primary data
Incidence of TB at CD4 <50	0.6060606	0.6060606	0.6060606	Primary data
Incidence of adverse effects for patient on long term ART[#]				
Hepatitis	0.084286607	0.08217944	0.08639377	Primary data
Anaemia	0.038378308	0.03741885	0.03933777	Primary data
Lipodystrophy	0.014568151	0.01420395	0.01493236	Primary data
Skin reaction	0.177717101	0.17327417	0.18216003	Primary data
GI disturbances	0.024162154	0.0235581	0.02476621	Primary data
IRIS	0.028924072	0.02820097	0.02964717	Primary data

Contd...

Parameter	Value	Lower limit	Upper limit	Source reference
Incidence of adverse effects for patient on long term ART[#]				
Discount rate (%)	0.03	0.01	0.07	22
Cost/year (ART) (varied following gamma distribution)				
Tertiary care centre (per year per patient)	45,105	12,177	12,177	15
ART centre (per year per patient)	24,945	7123	7123	15
Weighted average cost/year/patient (ART)	28,996	21,747	36,245	15
Cost/year (pre-ART) (varied following gamma distribution)				
Tertiary care centre (per year per patient)	12,177	12,177	12,177	15
ART centre (per year per patient)	7123	7123	7123	15
Average cost/year/patient (pre-ART)	8248	6186	10,310	15
Cost of management of herpes infection/patient/year or episode	1828	810	6983	16
Cost of management of other viral infection/patient/year or episode	1828	810	6983	16
Cost of management of candidiasis/patient/year or episode	1828	810	6983	16
Cost of management of TB/patient/year or episode	3980	2985	4975	17
Cost of management of malignancies/patient/year or episode	28,295	21,221	35,368	18
Cost of management of ADRs (varied following gamma distribution)				
Hepatitis/patient/year or episode	858	836.55	879.45	10
Anaemia/patient/year or episode	858	836.55	879.45	10
Lipodystrophy/patient/year or episode	858	836.55	879.45	10
Skin reaction/patient/year or episode	858	836.55	879.45	10
GI disturbances/patient/year or episode	9372	9137.7	9606.3	10
IRIS/patient/year or episode	858	836.55	879.45	10
Utility weights				
CD4 >500	0.946	0.924	0.964	13
CD4 500-351	0.933	0.914	0.951	13
CD4 350-201	0.931	0.914	0.951	13
CD4 <200	0.853	0.835	0.865	13
CD4 <50	0.781	0.781	0.781	13

IRIS, immune reconstitution inflammatory syndrome; ART, antiretroviral therapy; ADRs, adverse drug reactions; TB, Tuberculosis; GI, gastrointestinal

all other expenditures combined, *viz*. treatment of OIs and management of complications and adverse effects of antiretroviral drugs as summarized in Table IV. If implemented with immediate effect across the PLHIV registered with NACO, the test and treat strategy will put extra budgetary impact (estimated using HTAIn Budgetary Impact Assessment Guidelines[20]) of ₹ 1382.10 million on the first year. Subsequently, the figure may decrease with 1047.20 million in second year and 804.10, 624.70 and 492.00 million in the third, fourth and fifth year, respectively.

Effects/consequences: As expected, there was a reduction in the number of new HIV infections through heterosexual population due to the effect of ART. Considering reported levels of adherence to ART, new HIV transmissions were estimated to be minimum, *i.e*. 0.23 million in the test and treat scenario as compared to Scenario II and III as depicted in Table IV. A total of 16,105 new HIV infections were averted by implementing the test and treat over Scenario II and as 74,875 new HIV infections were averted over Scenario III. Initiating ART earlier also increases the overall life expectancy of HIV patients due slow progression of disease and hence reduction in HIV-related deaths. By implementing test and treat, life expectancy increased by 0.17 years over Scenario II and by 0.60 years over Scenario III. HIV-related deaths during the

Table IV. Costs, effects and cost-effectiveness of alternative strategies for antiretroviral therapy treatment initiation

Characteristics	Scenario I (test and treat)	Scenario II (ART initiation at CD4 <500 mm^3)	Scenario III (ART initiation at CD4 <350 mm^3)
Health effects			
New HIV transmissions	230,534	246,639	305,409
HIV deaths	209,391	227,778	270,559
Life years lived (Cohort)	13,776,115	13,634,969	13,292,810
QALYs lived (Cohort)	12,919,793	12,576,620	12,183,266
Costs incurred (₹ in million)			
ART	3,485,42	3,262,72	2,746,94
Others	191,20	253,79	338,77
Total	3,676,63	3,516,51	3,085,71
Incremental cost (₹) per QALY gained			
Scenario I versus II		46,599	
Scenario I versus III		80,050	
Scenario II versus III		109,233	

ART, antiretroviral therapy; QALYs, quality-adjusted life-years

given time horizon in Scenario I were 0.209 million as compared to 0.227 million in Scenario-II and in 0.270 million in Scenario III, respectively as depicted in Table IV and Supplementary Table I. Apart from the difference in years of life lived by PLHIVs in all three scenarios, a substantial difference in the quality of life of HIV patients was estimated, as highlighted in the Supplementary Table II. The number of QALYs lived in the 'test and treat' scenario as compared to Scenario-II and III was ascertained to be 12.91, 12.57 and 12.18 million, respectively in lifetime horizon as depicted in the Supplementary Table III.

Cost-effectiveness: To compare health outcomes and costs in all three scenarios of our analysis, ICERs were calculated. Extra cost incurred by implementing test and treat over Scenario II and III was compared with QALYs gained over these scenarios to get the results in the form of cost per QALY gained. After discounting, test and treat was estimated to have ICER of ₹ 46,599 per QALY gained as compared to Scenario II. This ICER was about one third of per capita GDP of India in financial year 2017-2018. Test and treat when compared to Scenario III, was estimated to have ICER of 80,050 per QALY gained which again was less than the then per capita GDP of India. ICER of Scenario II over Scenario III was estimated, which came around to be 0.10 million per QALY gained; again, less than per capita GDP of India. Discounted ICERs for various scenarios are also summarized in Table IV.

Sensitivity analysis: One-way sensitivity analysis run for all the input parameters found that three input parameters, *viz*. - cost of ART, cost of pre-ART and discount rate have the maximum impact on the cost-effectiveness of the intervention. Seven parameters sorted according to their impact on ICER in the decreasing order are used to construct a tornado chart as shown in Fig. 2.

PSA done using randomly selected values using beta distribution for probabilities, utility values and proportions; gamma distribution for all cost parameters. After 1000 simulations using visual basics, results plotted as cost-effectiveness acceptability curve and cost-effectiveness plane are given in Figs. 3 and 4.

Considering all uncertainties involved with estimation of input parameters, it was found that the of test and treat strategy cost may be effective with a 100 per cent probability and at a willingness-to-pay threshold equal to per capita GDP of India.

Discussion

This study was done to assess the cost-effectiveness of the test and treat strategy as per the recommendations of WHO. As evident from the results, the test and treat intervention falls under highly cost-effective interventions (based on cost-effectiveness threshold of and WHO[21] and HTAIn[22]) in the Indian context with ICER less than the per capita GDP of India. This cost-effectiveness is largely due to decreased burden of OIs

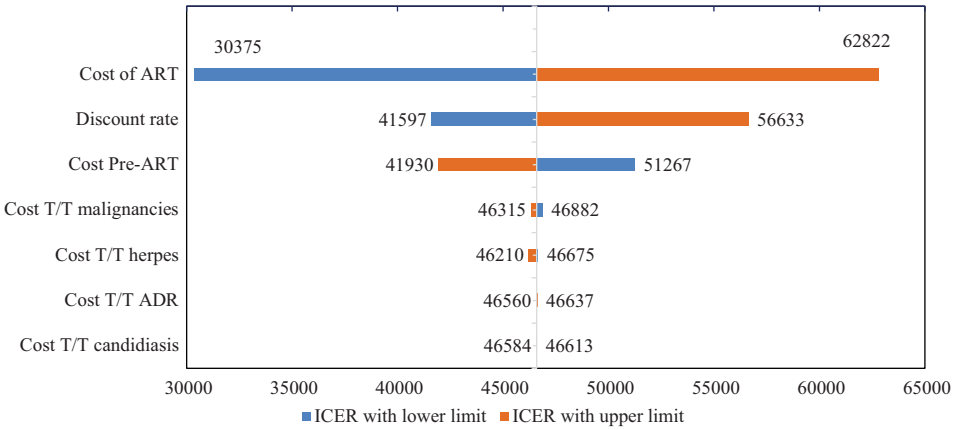

Fig. 2. Tornado chart of one-way sensitivity analysis (OWSA) using lower and upper bound of input parameters. ART, antiretroviral therapy; ADR, adverse drug reaction; t/t, test and treat; ICER, incremental cost-effectiveness ratio.

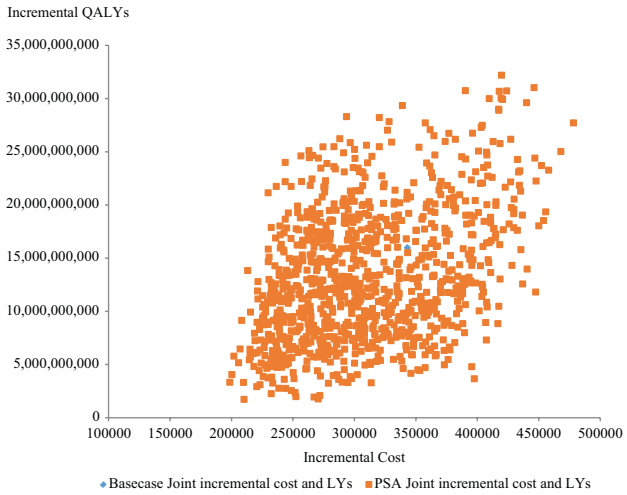

Fig. 3. Cost effectiveness plane cloud for 1000 iterations of incremental cost and QALYs gained. CE, cost-effectiveness; ART, antiretroviral therapy; QALYs, quality adjusted life years; PSA, probabilistic sensitivity analysis; LYs, life years.

and averted new HIV cases. Our analysis estimates that, a total of 23,472 new infections can be averted by implementing test and treat, as depicted in the supplementary Table IV. This decrease in new infections can be a significant cost saver as the health system then has to incur less costs to treat new PLHIVs in the future.

In addition, an increase of 0.26 years in life expectancy per HIV patient was estimated by our analysis which then gets translated in additional 0.246 QALYs lived per person in comparison to Scenario II. This increase in life expectancy and quality of life due to early initiation of ART can then be compared to the costs to ascertain its value for money. Positive impact of test and treat may also be due to a reduction in the load of OIs and can further increase over time based on the cumulative averted HIV infections.

Two economic evaluations of changes in strategy for the initiation of ART have been reported previous[10,11]. Eaton *et al*[10] reported the test and treat to be cost saving over a time horizon of five years as compared to the initiation of ART below a CD4 count of 350/mm^3, while Maddali *et al*[11] found early ART (above CD4 count of 350/mm^3) in current care continuum as compared to delayed ART (CD4 count of 350/mm^3) to be cost-effective over the time horizon of 20 years with an incremental cost of US$ 442 per QALY gained.

The present analysis has several strengths. First, as compared to previous analyses which used either financial cost of ART delivery or some other proxy data for costing[10,11], we used cost inputs from a local economic costing analysis of ART delivery[15]. This cost analysis also factors in the proportion of patients developing resistance to first line therapy, and hence, cost of second or third line therapy, which is significantly higher than the first line therapy[15]. Second, this study estimated the transition probabilities, based on the analysis of follow up data of Indian HIV patients. However, the data include representation from the northern regions such as Punjab, Haryana, Chandigarh in Himachal Pradesh, Rajasthan, and Jammu and Kashmir. This study incorporates the realistic estimates by including patients at the reported level of adherence to the therapy along with those on second and third line ART therapy; however, to address the variation across States, we varied the adherence rate by 20 per cent on both sides for generalizability of results.

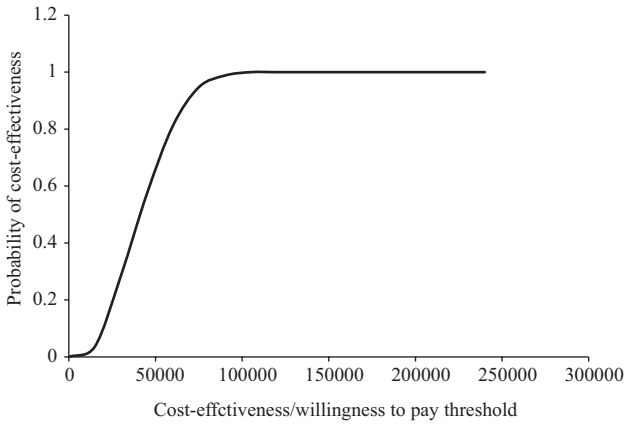

Fig. 4. Cost effectiveness acceptability curve (CEAC): Probability of cost-effectiveness and willingness to pay. QALYs, quality adjusted life years.

Rates of transmission of HIV were ascertained in our study by using Weinstein's equation which factors in several behavioural parameters specific to the Indian population[23]. Our model also incorporated the most common OIs and their effect on health utility weights as well as cost of care due to early initiation of ART, which is a life long therapy and cannot be stopped once started. As a result, chances of development of toxicity to first line therapy and adverse effects can be a major issue, which was incorporated in our model.

Despite the strengths, the study also had some limitations. This is, however, acknowledged as a limitation that the data used to calculate transition probabilities are assumed to represent the national population as this is the first evaluation which uses local data on clinical effectiveness of ART. Furthermore, the adherence to the therapy could be different in other regions such as the southern States of the country; therefore, it would impact the cost-effectiveness of intervention. The spectrum of OIs in HIV is wide, but only five potential OIs were considered to be modelled to avoid the complexity. In the selected OIs too, co-infections are possible in real-life situation. However, this was not included into the model in view of data limitations. It was assumed that all these infections, which were being covered are mutually exclusive and are independently occurring in case of HIV infection. We modelled only for the heterosexual route of subsequent transmission of HIV. This is likely to underestimate the cost-effectiveness of test and treat by not accounting for the reduced HIV transmission for MSM and injecting drug users. Finally, while major data used in parameters were local, quality of life data for the Indian population was not available in the literature. Hence, data from similar studies elsewhere were used as input to the model, which is a limitation and can impact the accuracy of ICER due to potentially different health preferences of the Indian population. It would also be valuable if some research on number of patients not registered with NACO is undertaken in the future. This will help to give more accurate estimates about cost-effectiveness of test and treat. Furthermore, this analysis only covers public sector patients in terms of cost, clinical impact and the overall cost-effectiveness in the private sector could be different. Cost of service delivery in the private sector is comparatively more, which means, if we assume a scenario where more patients start availing services from public health facilities through NACO, the ICER would be further lowered, *i.e*. the intervention would become more cost effective.

The implementation of test and treat will substantially increase the cost of care and support for India's HIV control programme in the short run, but in later years, the total cost incurred by healthcare will decrease drastically. Hence, test and treat should be considered as a long-term investment in healthcare. Our model suggests that, at the reported rates of adherence to ART, many potential benefits of this policy will remain unexplored. As cost of delivery of ART through a tertiary care centre is found more than that of other ICTCs; patients receiving ART from tertiary care settings and CoEs must be kept low. It can be further reduced by linking maximum patients to link ART or ART centres to further reduce the overall cost of delivery of ART. Major expenditure on the delivery of ART to patients is of antiretroviral drugs; so, government can make efforts to further reduce the cost by amendments in procurement. As evident form the transition matrix developed and used in this study, the mortality was high in the advanced stages of HIV with low CD4 count; efforts must hence be made to diagnose and link the HIV patient to the treatment at the early stages of infection. This will reduce the HIV-related mortality and OI and hence the overall cost incurred by the health system.

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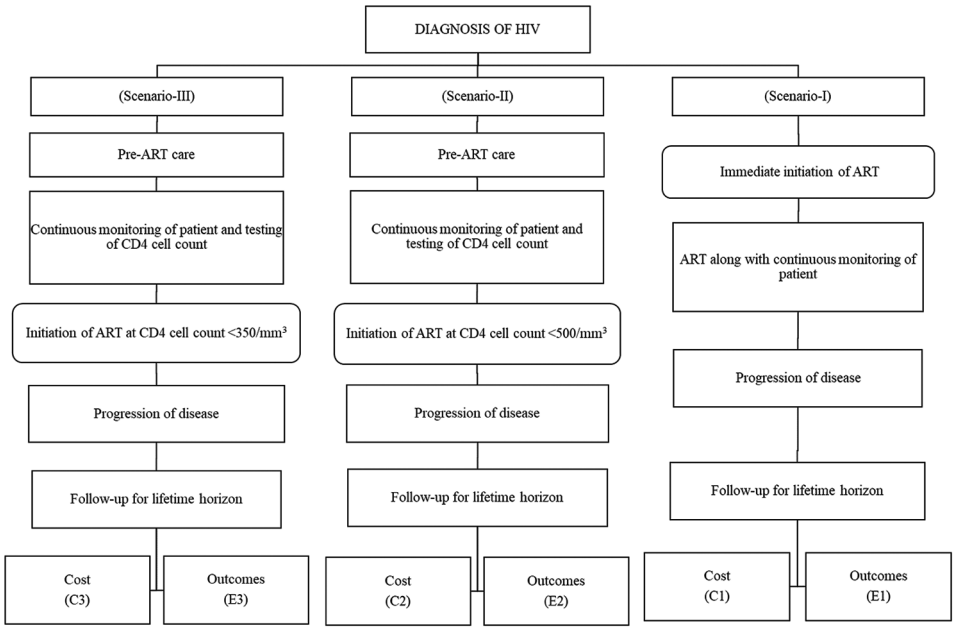
Supplementary Material



Supplementary Fig. 1. A brief outline of 3-arm modelling design (conceptual framework) of the evaluation.

Calculation of new human immunodeficiency virus infections

Weinstein's equation[14] was used to calculate the average per person year probability of heterosexual transmission of human immunodeficiency virus (HIV) from infected person to uninfected population using various characteristics of Indian people living with HIVs (PLHIVs) and general population as input parameters from literature. Factors considered while calculating average transmission probability of a PLHIV were annual sexual partnerships per year, type of partnership *i.e*. whether with spouse or casual sex or with FSW, type of sexual contacts i.e. anal, oral and vaginal), infected partner (male or female), condom use and status of antiretroviral therapy whether on antiretroviral therapy i.e. on ART or not on ART *etc*.

Weinstein equation;

$$\rho = 1 - [\Pi\,(1 - \lambda_{\varphi k \lambda}\,(1 - \phi \times \varepsilon))^{N} + (1 - \Pi)]^{M}$$

Where,

ρ=Annual prob. of HIV transmission/individual.

Π=Prevalence of HIV in partner group.

$\lambda_{\varphi k \lambda}$=Transmission coefficient per sex act based on type of sex act (k)

STD status (j) of recipient and direction of transmission (l).

ϕ=Proportion condom use.

ε=Efficacy of condom.

N=Number of sex acts per partner per year.

M=Number of sex partners per year.

Estimation of costs

The overall cost summed up (Fig. 2) as per following equation:

Overall Cost = Cost due to increased patient load
+ Cost due to longevity of treatment
− Cost saved by less expenditure on Pre-ART care and OIs.
− Cost saving by reduction in the treatment costs associated with reduction in transmission of HIV.

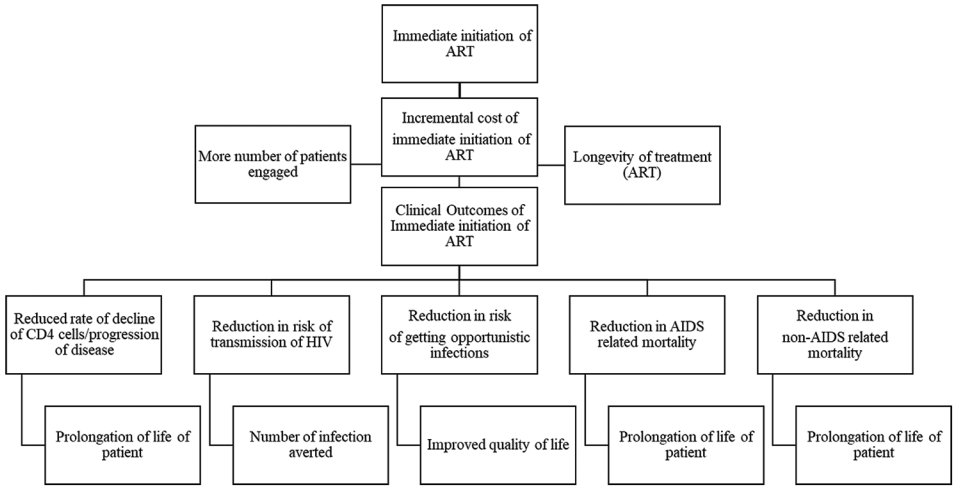
Calculation of transition probabilities

Transition probabilities for moving from one stage to another stage were calculated using data obtained from data centre of Centres of Excellence, running in a tertiary care centre of North India. Both the Pre-ART and ART patients data were taken form data centre and rates of transition from one stage to another stage were noted. Patient, whose transitions were recorded, was adults form age 15-49 and were regular on follow-up. By applying filter in the Microsoft Excel, only relevant patients were selected. Exclusion criteria during analysis were;

1. Children or younger adults (<15 yr)
2. Ones, whose ART was stopped due to any reason
3. Patients, who were not regular with the follow-up of treatment and care services
4. Those, whose status of CD4 count was unknown due to any reason.

Ultimately, records of 1453 patients on follow up were traced. Total five categories were made according to CD4 count (CD4 count >500/mm^3, CD4 count 500-350/mm^3, CD4 count 350-200/mm^3, CD4 count 200-50/mm^3 and CD4 count <50/mm^3). Then rates of progression and regression to different disease states were calculated through their CD4 count at exactly 6 months from their first CD4 count and then, these six monthly rates were converted into one yearly rates. Rates of transition from one stage to another in one year are given in Supplementary Table I.

Similarly, records of patients on Pre-ART care also were analyzed to obtain transition rates of patients who are not on ART. Because most of patients at present were started on ART due to implementation of new policy of NACO to immediately start the ART drugs to all patients regardless of CD4 count or WHO clinical stage, the records were analyzed from 2016, when criteria to initiate ART was drop of CD4 count below 350/mm^3. Patients with CD4 count more than 350/mm^3 or those not on ART due to any other reason like toxicity or unwillingness to take drugs etc., were included in this phase of analysis. Same filters were applied by the help of Microsoft Excel to exclude the children or younger adults lesser than 15 years of age; ones whose ART was stopped or altered due to any reason; ones less regular to the follow-up to treatment; and those whose status of CD4 count was unknown due to any



Supplementary Fig. 2. Costs and outcomes: An overview.

reason. Total 776 patients on Pre-ART care or without ART drugs were found eligible for the calculation of rates of transition. CD4 count at a particular point time and then exactly 6 months after the first CD4 count was recorded. Here also, 6 monthly transition rates were calculated at first and then by the help of mathematical model, 1 yearly rates were obtained. Results from this analysis are as given in Supplementary Table II.

Results: Health Outcomes

Additional results from our model, in relation to different scenarios based on difference due to different timings of the initiation of CRT are summarised in following Supplementary Tables I to V.

Results: Costs

Estimated costs in different scenario, corresponding to the actual number of PLHIVs on ART and infection rates etc. are hereby summarized in following Supplementary Tables VI to VIII.

Supplementary Table I. Estimated human immunodeficiency virus-related deaths across different scenarios in 20 yr time horizon

ART initiation criteria	HIV related deaths
Scenario-I	209,391
Scenario-II	227,778
Scenario-III	270,559

HIV, Human immunodeficiency virus; ART, antiretroviral therapy

Supplementary Table II. Life years lived by 1,141,531 people living with human immunodeficiency virus over 20 yr in all three different scenarios

ART initiation criteria	Life years lived (million)	
	Undiscounted	Discounted
Scenario-I	17.56	13.77
Scenario-II	17.37	13.63
Scenario-III	16.87	13.29

ART, antiretroviral therapy

Supplementary Table III. Quality adjusted life years lived by 1,141,531 people living with human immunodeficiency virus over 20 yr

ART initiation criteria	Quality adjusted life years lived (in million)	
	Undiscounted	Discounted
Scenario-I	16.46	12.92
Scenario-II	16.28	12.57
Scenario-III	15.80	12.18

ART, antiretroviral therapy

Supplementary Table IV. Estimated new human immunodeficiency virus infections across different scenarios of antiretroviral therapy initiation over 20 yr

ART initiation criteria	Estimated total new HIV infections			
	Ideal scenario		Realistic scenario*	
	Undiscounted	Discounted	Undiscounted	Discounted
Scenario-I	112,418	87,614	230,534	178,625
Scenario-II	132,724	105,869	246,639	192,998
Scenario-III	208,299	165,899	305,409	239,553

*At reported rates of adherence. ART, antiretroviral therapy

Supplementary Table V. Estimated health outcomes in new human immunodeficiency virus infections during their lifetime horizon

ART initiation criteria and comparator	Estimated health outcomes (realistic scenario)			
	Life years saved		Quality adjusted life years saved	
	Undiscounted	Discounted	Undiscounted	Discounted
Scenario-I versus Scenario-II	194,694	141,146	185,693	343,173
Scenario-I versus Scenario-III	689,717	483,305	658,771	736,527
Scenario-II versus Scenario-III	495,024	342,159	473,078	393,354

ART, antiretroviral therapy

Supplementary Table VI. Estimated cost of delivery of antiretroviral therapy to people living with human immunodeficiency virus in different scenarios over 20 yr

ART initiation criteria and comparator	Estimated costs#			
	Idealistic scenario		Realistic scenario*	
	Undiscounted	Discounted	Undiscounted	Discounted
Scenario-I	5,327,53	4,175,84	4,104,96	3,217,16
Scenario-II	5,111,99	3,989,34	3,956,10	3,089,12
Scenario-III	4,395,89	3,427,98	3,465,95	2,706,10

*At reported rates of adherence; #Costs in million ₹. ART, antiretroviral therapy

Supplementary Table VII. Estimated costs incurred on new human immunodeficiency virus infections during their life-time horizon

ART initiation criteria and comparator	Estimated costs[#]			
	Idealistic scenario		Realistic scenario[*]	
	Undiscounted	Discounted	Undiscounted	Discounted
Scenario-I	496,71	304,90	779,23	476,42
Scenario-II	515,72	314,42	737,21	444,54
Scenario-III	508,09	358,96	566,30	397,88

[*]At reported rates of adherence; [#]Costs in million ₹. ART, antiretroviral therapy

Supplementary Table VIII. Breakdown of total cost incurred by healthcare system in immediate antiretroviral therapy scenario

Health system cost heads	Percent share
ART cost	96.954
Management of herpes infections	0.168
Management of other viral infections	0.180
Management of malignancies	0.103
Management of candidiasis	0.195
Management of TB	0.349
Management of ART complications	2.048

ART, antiretroviral therapy; TB, tuberculosis