TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS WITH ZIDOVUDINE AND TENOFOVIR REGIMEN IN INDIA: A COMPARATIVE EFFECTIVENESS STUDY

A thesis

submitted by

SOWMYANARAYANAN THUPPAL, MD

In partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

IN

CLINICAL AND TRANSLATIONAL SCIENCE

TUFTS UNIVERSITY

SACKLER SCHOOL OF GRADUATE BIOMEDICAL SCIENCES

May 2015

ADVISORS

Thesis Chair: Christine A Wanke, MD
Project Mentor: Mkaya Mwamburi, MD PhD
Project Mentor: Joshua T. Cohen, PhD
Statistical Mentor: Farzad Noubary PhD
External Advisor: Jayaprakash Muliyil MD DrPH

DEDICATION

This PhD dissertation is dedicated

To my most wonderful parents in the World

For your unconditional love and affection
For your wholehearted support and guidance
For your unlimited sacrifice and dedication
For your devoted nurture and care

Without which I certainly would not be where I am today!

Thank you Amma (Mom) and Appa (Dad)

TO KAMALA AND VARADACHARI THUPPAL

ABSTRACT

Human Immunodeficiency Virus (HIV) is one of the leading causes of death among infectious diseases. The adult HIV prevalence in India is around 0.27%. Combination anti-retroviral therapy (ART) with tenofovir as a component is considered to be the most efficient drug regimen along with emtricitabine and efavirenz. However in resource limited settings, this combination is not preferred since it is considered very expensive. Inspite of higher rates of drug related toxicities zidovudine containing regimen with lamivudine and nevirapine is considered the first-line treatment of choice in resource limited settings, since they are less expensive. Comparative effectiveness studies from resource sufficient settings show that tenofovir containing regimen is the better treatment for HIV. But country specific studies are required to compare these two regimens and identify the best treatment for that setting. Hence the objective of this PhD dissertation is to compare the economic, clinical and quality of life outcomes in patients living with HIV on treatment with zidovudine (along with lamivudine and nevirapine) and tenofovir (emtricitabine and efavirenz) regimens from an infectious disease clinic, at a private tertiary care hospital in southern India.

To achieve this objective we conducted four different projects: The first project documented the toxicities and the cost of treatment for six months in patients living with HIV, initiated on the current first-line zidovudine containing regimen. The study showed that approximately 30% of the patients experienced drug related toxicity. Overall costs spent on treatment for a period of six months excluding antiretroviral drugs (antiretroviral drugs are provided free of costs to patients by the government) was Indian Rupees (INR) 7,157, which was one-third the average income earned by the patients during the study period. Exploratory analysis comparing treatment costs, including both direct and indirect costs showed that, patients with drug related toxicities had to spend significantly more than patients without drug related toxicities, imposing an additional significant economic burden to the patients.

In the second project we compared the data collected from patients initiated on both the regimens prior to implementation of the government sponsored free antiretroviral therapy program. Patients who could afford to pay opted for the expensive tenofovir containing regimen, while those who could not afford opted for a less expensive zidovudine containing regimen. Since our study was observational and ability to pay may have been associated with both selection of treatment regimen and other characteristics potentially influencing health, we used propensity score (PS) analysis to mitigate the potential confounding. Compared to patients receiving zidovudine regimen, patients receiving tenofovir regimen had fewer adverse drug reactions (47% vs. 11%, p-value: <0.01), requiring fewer regimen changes (36% vs. 3%, p-value <0.01). With PS, zidovudine regimen had 8 times more adverse drug reactions (p-value: <0.01). Opportunistic infections were similar between regimens without PS, while zidovudine regimen had 1.2 times (p-value: 0.63) more opportunistic infections with PS. Patients on tenofovir regimen gained more body mass index. Increase in CD4 levels and treatment adherence (>95%) was similar across regimens. Patients on a tenofovir regimen had better clinical outcomes with improved general health than patients on zidovudine regimen.

The third project was a pragmatic randomized clinical trial comparing treatment naïve HIV positive patients started on zidovudine and tenofovir containing regimens based on costs, clinical and quality of life outcomes. Compared to patients on the zidovudine regimen patients on the tenofovir regimen had significantly fewer adverse drug reactions (89% vs 45%, p-value: <0.01) and required fewer regimen changes (35% vs 7%, p-value: <0.01). The proportion of patients on zidovudine regimen experiencing opportunistic infections exceeded the corresponding proportion for patients on the tenofovir regimen (46% vs 31%, p-value: 0.22). Patients on the tenofovir regimen tend to have better quality of life and improved CD4 values than patients on the zidovudine regimen. Overall treatment costs did not differ between the two regimens, however

the cost of treatment in patients with adverse drug reactions or opportunistic infections or both was greater in patients receiving zidovudine regimen compared to those receiving tenofovir regimen. The study findings suggest that compared to zidovudine regimen, the tenofovir regimen has fewer adverse drug reactions and opportunistic infections with greater improvement in CD4 levels and quality of life.

Fourth project was a cost effectiveness analysis between zidovudine vs. tenofovir regimens. Model parameters including median costs, quality adjusted life years from SF6D and EQ5D questionnaires, and transitional probabilities were obtained from the pragmatic randomized study (project 3). A decision tree analysis was performed to estimate the cost effectiveness for a period of one year. A Markov decision model was performed for calculating the long term incremental costs and quality adjusted life years. From payer perspective the tenofovir-containing regimen cost 8,091 Indian Rupees and conferred a health benefit of 0.02 QALYs compared to the zidovudine-containing regimen, yielding a cost-effectiveness ratio of 404,550 INR (6,525 USD) per QALY. The Markov model projected an incremental cost of 1,768,298 INR (USD 28,521) and an incremental health gain of 0.08 QALYs. From the patient perspective, the tenofovir-containing regimen reduced costs and improved health (decision tree analysis: 4,596 INR saved and 0.01 QALYs gained; Markov model: 44,413 INR saved and 0.08 QALYs gained). Based on the WHO-CHOICE criteria for cost effectiveness analysis, tenofovir-containing regimen was not cost effective with payer perspective, however was cost effective with patient perspective.

In conclusion, this PhD dissertation comparing zidovudine and tenofovir containing regimens for HIV in India suggest that: Fewer proportions of patients on the tenofovir regimen had adverse drug reactions and opportunistic infections compared to zidovudine regimen. Cost of treatment due to adverse drug reactions and opportunistic infections and the necessity for regimen change

due to adverse drug reactions were higher in patients receiving zidovudine regimen than those patients receiving tenofovir regimen. From patient perspective tenofovir-containing regimen saved costs and improved health in patient living with HIV. Hence steps should be taken to reduce the procurement costs for the tenofovir-containing regimen and to implement the tenofovir-containing regimen as the first-line treatment regimen for patients living with HIV in India.

ACKNOWLEDGEMENTS

Completing my PhD was a dream come true and I am happy that I have successfully completed my PhD. Theoretically learning the basics of clinical research and practically reproducing the same in the real world setting was a challenge but at the same time most rewarding. It would have been more challenging to achieve my PhD without the constant support, guidance and encouragement from all the brilliant individuals and excellent institutions that I worked with and interacted with during the course of my PhD. Doing my research projects at Christian Medical College, Vellore, India and presenting my dissertation at Tufts University, in the United States, reiterates the long-lasting research collaborations between these two institutions, that has helped through my PhD.

There are many other people who contributed to my PhD and in writing this dissertation, in many ways. Though I cannot thank each one by name, I will forever be grateful to all. First I would like to thank two of my exceptional mentors Prof. Gagandeep Kang MD PhD and Prof. Christine A. Wanke MD. They are not just my mentors, but they are my guide and philosophers. William A. Ward said that a great teacher inspires and I can certainly say that the inspiration I got from these two great teachers has helped me reach this stage in my life. I would like to express my appreciation to Prof. Kang for trusting and providing me with the opportunity to pursue my PhD at Tufts University. I want to thank Dr.Wanke for offering invaluable guidance, helping me develop my PhD project, providing detailed comments and suggestions on this and other work, for her effective role as chair of my PhD committee and in offering me advice and guiding me in my academic carrier.

I would like to express my gratitude to Dr. Mkaya Mwamburi for his support and valuable contribution to my PhD and guiding me in my carrier path. I would like to thank Drs. Joshua T.

Cohen PhD and Farzad Noubary PhD for their technical and intellectual expertise and guidance in cost-effectiveness analysis and statistical methods and their support and persistence for excellence throughout my PhD. My gratitude also goes to Prof. John L. Griffith, Prof. Norma Terrin and Prof. Christina Holcroft for their expertise and thoughtful contributions. I am indebted for having an exceptional PhD committee and in particular, for all the hours of meetings, consultations, tons of pages of editing, comments, insights and encouragement.

I would like to express my appreciation to Prof. O.C.Abraham, MD and thank him for trusting and providing me with the opportunity to conduct my PhD projects at the Department of Medicine Unit 1 and Infectious Diseases at Christian Medical College, Vellore, India. I would like to thank Prof. Jayaprakash Muliyil MD DrPH, Department of Gastrointestinal Sciences, Christian Medical College, Vellore, India for being my external mentor and providing timely suggestions and expertise for successful completion of my PhD.

I would like to thank Drs. Rajiv Karthik MD MPH and Ajay Rangaraj MBBS for their help in smoothly conducting my PhD projects. I would like to express my gratitude to Social workers Mr. Peace Clarance MSW, Mr. Gunaseelan Rathinam MSW and Mr. Michael Raj MSW, Pharmacists Mr. Rajkumar Sathasivam MPharm and Mr. Madhu Bhadra BPharm, Ms. Sathya RN and rest of the team in Vellore, India for their continued assistance and support during my PhD. I would like to thank all my study participants, for consenting to be part of my research and following study instructions and timely providing study related information.

I would like to thank current and past faculty and staff of the Sackler School of Graduate Biomedical Sciences, Clinical and Translational Science Program, Tufts University, including Prof. Harry P. Selker, MD MSPH, Prof. David M. Kent MD CM MS, Dr. Jessica Paulus ScD,

Prof. Karen Freund MD, Prof. Robert J. Goldberg PhD and Prof. Christopher H. Schmid PhD for their intellectual, scholarly and pedagogical support.

My special thanks to Ms. Nina Bonnoyer and Ms. Elizabeth Wiltrout, Clinical and Translational Science Program, Tufts University; Ms. Helen Arroyo, Ms. Catherine Gauthier and Ms. Brenda McGinnis, Nutrition/Infection Unit, Community Medicine and Public health, Tufts University for their administrative support and help throughout my PhD.

I would like to thank Brown/Tufts Fogarty AIDS International Training Program and Fogarty International Center for their fiscal support without which my PhD would not have been a possibility.

I would like to thank my parents Mrs. Kamala MA and Mr. Varadachari Thuppal BA BL, to whom this dissertation is dedicated. I thank my friends and colleagues for their support throughout the PhD.

I would like to thank my wife, Ms. Tanushree Thuppal for her support and understanding throughout my PhD. I like to thank my wonderful, kind and caring son Master Sricharan Thuppal for his support. He is and will be my inspiration in all my future endeavors.

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

ADR – Adverse Drug Reaction
AIDS –Acquired Immune Deficiency Syndrome
ALT –Alanine Aminotransferase
ART –Anti-Retroviral Therapy
AST –Aspartate Aminotransferase
AZT –Zidovudine
BMI –Body Mass Index
cART –combination Anti-Retroviral Therapy
CEA –Cost Effectiveness Analysis
CI –Confidence Interval
CMC –Christian Medical College
CMV –Cytomegalovirus
Co-OI –Co Opportunistic Infection
d4T –Stavudine
EFV –Efavirenz
EQ5D –European Quality of Life 5 Dimensions
FTC –Emtricitabine
FV –Future Value
GI –Gastro Intestinal
HIV –Human Immunodeficiency Virus
INR –Indian Rupees
IP –In Patient
IQR –Inter Quartile Range
MOS –Medical Outcomes Study
NACO –National AIDS Control Organization
NACP –National AIDS Control Program
NNRTI –Non-nucleoside Reverse-transcriptase Inhibitor
NRTI –Nucleoside Reverse-transcriptase Inhibitor
NVP –Nevirapine
OI –Opportunistic Infection
OR –Odds Ratio
PI –Protease Inhibitor
PS –Propensity Score
PV –Predictive Value
QALY –Quality Adjusted Life Year
QoL –Quality of Life
RLS –Resource Limited Setting
RSS –Resource Sufficient Setting
SAS –Statistical Analytical System

SD –Standard Deviation
SE –Standard Error
SF6D –Medical Outcomes Study Short Form 6 Dimensions
TB –Tuberculosis
TDF –Tenofovir
WHO –World Health Organization

INTRODUCTION

1.1 OVERVIEW

Human Immunodeficiency Virus (HIV) is one of the leading causes of death among infectious diseases. Timely and appropriate initiation of treatment reduces morbidity and mortality, reduces the transmission of infection and improves quality of life in patients living with HIV. A combination anti-retroviral drug regimen containing tenofovir along with emtricitabine and efavirenz is the recommended first line treatment for HIV by World Health Organization. However in resource limited settings, this combination is not generally used since it is considered expensive. Despite the higher rates of drug related toxicities a zidovudine, lamivudine and nevirapine containing regimen is considered the first-line treatment of choice in resource limited settings, since it is less expensive. In India steps are being taken to adopt the tenofovir-containing regimen as the first-line treatment through the free government sponsored antiretroviral program. However, for policy making, it is essential to compare tenofovir- and zidovudine-containing regimen based on the treatment costs as well as the effectiveness of the two regimens.

1.2 HIV EPIDEMIOLOGY

Globally, approximately 35 million people were infected with HIV at the end of 2013. In India, the number of people living with HIV in 2013 was 2.1 million (1.7-2.7 million) corresponding to an estimated adult HIV prevalence of 0.27 % (0.2%-0.3%) [1-3]. Evidence suggests a declining trend in the adult HIV prevalence percentage in India from 0.33% in 2007[1]. In India heterosexual sex is the major route of transmission accounting for 87% of HIV cases detected[1]. Intravenous drug use is the major route of transmission in the north-eastern part of India. India has the third highest global HIV prevalence next to South Africa and Nigeria.

1.3 INITIATION OF ANTIRETROVIRAL THERAPY

Initiation of antiretroviral therapy depends on the HIV status, and is most commonly decided by CD4 count and severity of disease. According to the World Health Organization guidelines 2013, antiretroviral therapy should be initiated in adults if the CD4 cell count falls below 500 cells /µl. The World Health Organization also recommends the rapid initiation of antiretroviral therapy in patients living with HIV with active tuberculosis disease or Hepatitis B co-infection and in serodiscordant couples (one partner among the couples is positive for HIV while the other is negative for HIV) and in pregnant and breastfeeding women[4]. Studies have shown that early initiation of antiretroviral therapy reduces the risk of death[5-9] and decreases the risk of HIV progression[10,11]. Evidence suggests that early initiation of ART not only decreases the risk of tuberculosis [12], but also prevents recurrence of tuberculosis[13] leading to a reduction in the incidence of tuberculosis in a population[14]. Early initiation of antiretroviral therapy reduces the risk of sexual transmission of HIV to HIV-negative sexual partners[10]. In general, the WHO recommends initiation of therapy at an early stage of disease to prevent transmission of disease and maintain good quality of life.

In resource limited settings including India, however, treatment is initiated when baseline CD4 falls only below 350 cells/ µl and in all individuals with severe or advances disease irrespective of CD4 count. Priority is given to all pregnant and breastfeeding women. Increasing the CD4 cut off for treatment initiation from 350 cells/ µl to 500 cells/ µl significantly increases the number of people needing treatment[15]. This has an impact on the financial resources required to treat HIV. Financial constraints impact procurement and distribution of drugs. If patients living with HIV need to pay for antiretroviral therapy, then this cost may impact the willingness to initiate antiretroviral therapy as well as adherence to treatment. If the government provides the antiretroviral therapy, there must be assurance that the supply is sufficient and at hand. Hence in

resource limited settings, early initiation of antiretroviral therapy must be implemented with caution. It is crucial for countries to work toward early initiation of antiretroviral therapy for HIV. Therefore, country specific data on cost and cost effectiveness are important.

1.4 ANTIRETROVIRAL THERAPY

The goal of antiretroviral therapy is to achieve suppression of viral replication to the extent possible, to improve quality of life and to prevent emergence of drug resistance. Studies[16-20] have shown that combination retroviral therapy is superior to mono or dual therapies in achieving these goals. In 1996 World Health Organization recommended use of combination antiretroviral therapy for treating HIV infection. These approved regimens include combination of two nucleoside reverse transcriptase inhibitors (NRTI) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor[4]. According to WHO guidelines tenofovir along with emtricitabine and efavirenz is the recommended first line treatment, while zidovudine along with lamivudine and nevirapine is the alternative rgimen[4]. In the year 2010 the World Health Organization recommended that stavudine-containing regimens should be discontinued as the first line regimen due to its serious adverse drug reactions including lactic acidosis, neuropathy and lipodystrophy, especially fat atrophy [21].

In India, a government sponsored free antiretroviral therapy program was initiated in 2004 and by 2014 approximately 770,000 patients living with HIV were initiated on antiretroviral therapy[22], corresponding to 55% of patients eligible for initiation of antiretroviral therapy (1.1 million) as per Government of India recommendations. Until 2013, stavudine-containing regimens remained as the first line antiretroviral therapy regimen along with zidovudine-containing regimens. Tenofovir-containing regimens replaced stavudine-containing regimens as an alternative first line treatment[23] in 2013. Currently zidovudine along with lamivudine and

nevirapine is the first line regimen and tenofovir along with emtricitabine and efavirenz is the alternative drug regimen. The cost of tenofovir is part of the reason for reluctance to include it in first line treatment.

1.5 DRUG RELATED TOXICITY

One of the major complications with antiretroviral therapy is the occurrence of adverse drug reactions which may compromise quality of life and if severe, may require a regimen change. Based on research , the World Health Organization characterized the possible adverse drug reactions associated with antiretroviral drugs and their suggested regimen changes[24]. Some of the common side effects and the corresponding antiretroviral drug include:

Table 1 Adverse drug reactions associated with antiretroviral drugs

Drug	Adverse drug reaction
Abacavir	Hypersensitivity reaction
Zidovudine	Anemia, and neutropenia
Stavudine	Peripheral neuropathy, lactic acidosis and lipodystrophy
Tenofovir	Tubular renal dysfunction, Fanconi's syndrome, lactic acidosis, decreased bone mineral density
Efavirenz	Abnormal dreams, depression or mental confusion and male gynecomastia
Nevirapine	Hepatotoxicity, skin rash and hypersensitivity reactions
Etravirine	Hypersensitivity reactions
Darunavir/ritonavir	Hepatotoxicity and hypersensitivity reactions
Lopinavir/ritonavir	QT interval prolongation, hepatotoxicity and pancreatitis
Atazanavir/ritonavir	Clinical jaundice and nephrolithiasis
Raltegravir	Myalgia, myopathy and rhabdomyolysis

Studies have shown that the rate of patients experiencing adverse drug reactions on a zidovudine-containing regimens range from 15 percent to 50 percent[25-27]. Studies from resource sufficient

settings have demonstrated that the proportion of patients developing adverse drug reactions with the tenofovir-containing regimens range from only one percent to five percent[28-30].

A South African study demonstrated that tenofovir-containing regimen is associated with fewer toxicity related regimen switches and lower rates of loss-from-care when compared to zidovudine-containing regimen [31]. Another study from Lesotho demonstrated that toxicity related treatment change was two times greater among patients on a zidovudine-containing regimen than among patients on tenofovir-containing regimen [32]. A multicenter randomized trial comparing a tenofovir vs zidovudine containing regimen showed that the tenofovir-containing regimen has similar efficacy, but better safety outcomes than zidovudine-containing regimen[33]. While a Cochrane review comparing zidovudine- and tenofovir-containing regimens showed that adverse drug reactions and virologic responses were similar between these two regimens, the tenofovir-containing regimens was found to be superior to the zidovudine-containing regimens in terms of immunological response and adherence [34]. A non-inferiority randomized trial comparing the tenofovir regimen to the zidovudine regimen concluded that the tenofovir-containing regimen is superior to the zidovudine-containing regimen in terms of virologic suppression, change in CD4 and adverse drug reactions[35]. Overall, patients initiated on a tenofovir-containing regimen experience fewer adverse drug reactions and trend towards better adherence, better improvement in CD4 values and virologic suppression compared to those on the zidovudine containing regimen. Despite all these evidences, the tenofovir-regimen is not part of a first line treatment regimen in the Government of India antiretroviral program. To our knowledge we are providing the first data from India that directly compares tenofovir- and zidovudine-containing regimen in clinical, QoL and economic outcomes.

1.6 OPPORTUNISTIC INFECTIONS

The opportunistic organism is one that takes "the opportunity" to cause disease in an immunocompromised patient when it would not cause disease in a normal host. But infections in HIV may be caused by either opportunistic or a non-opportunistic organisms depending on how immunocompromised the host is[1,36]. Until the implementation of effective treatment for opportunistic infections and active scale-up of antiretroviral therapy, opportunistic infections were the major cause of morbidity and mortality in patients living with HIV[37]. There is a strong correlation between developing opportunistic infections and CD4 cell count in patients with HIV[1,36]. Patients can develop tuberculosis, oral candidiasis and herpes zoster infections when the CD4 falls below 500 cells/ µl. More severe and life threatening infections including *Pneumocystis* pneumonia, cryptosporidiosis, mycobacterium avium complex, cryptosporidiosis, cryptococcosis, toxoplasmosis and mucocutanious candidiasis and herpes infections develop when the CD4 falls below 200 cells/µl. Tuberculosis, candidiasis and cryptosporidiosis are the most common three opportunistic infections seen in India. Patients with opportunistic infections may also acquire sexually transmitted disease more frequently and these may lead to faster disease progression and increase in HIV transmission[38,39]. Hence, timely initiation of chemoprophylaxis for opportunistic infections and early initiation of antiretroviral therapy (initiation of therapy when CD4 counts falls below 500 cells/ µl) can reduce the morbidity[12,14] and mortality[5-8] in patients living with HIV as well as decrease transmission of HIV disease[10].

1.7 ADHERENCE TO TREATMENT

Adherence to treatment refers to the timely intake of prescribed medications in the appropriate dosage[40]. Studies have shown that patients with acute conditions have higher levels of adherence than patients with chronic disease[41]. In patients living with HIV, a serious chronic disease condition, it is very important to maintain a high degree of adherence to prevent emergence of resistance, disease transmission and progression. It is difficult to measure adherence to antiretroviral therapy as most methods are self-reported. Adherence can be measured as a categorical variable: adherence to treatment and non-adherence to treatment or can be measured as a continuous variable as percentage of adherence[42]. There are direct and indirect methods for measuring adherence[40]. Directly observed therapy, measurement of the level of antiviral or metabolite in blood or the measurement of a marker in blood are considered to be direct methods of measurement. Indirect methods include: patient interviews, pill counts, refill rates, clinical response to treatment, electronic monitoring and patient diaries. Measurement of the drug or its metabolites in blood and electronic monitoring are considered to be the most robust methods for assessing drug adherence, but in most resource limited settings these methods are not feasible since they are very expensive. Although most of the indirect methods are feasible to administrate in clinical research studies, they depend on the patients report and can give false results. In patients living with HIV measurement of viral load monitors the effectiveness of the treatment of HIV; if the viral load is undetectable, the regimen must be effective and the patient must be taking it regularly. Viral load measurement may be considered as the gold standard for clinical adherence assessment. But in resource limited settings viral load measurements are seldom feasible due to high costs. In resource limited settings adherence is measured by patient interviews, pill counts and clinical assessment. Studies have shown that better adherence to

antiretroviral therapy not only has positive impact on the CD4 count[43,44] but also on the quality of life[45]of the people living with HIV. Antiretroviral therapy regimens that are easier to take (fewer pills and smaller size) with few side effects are likely to be of benefit to adherence. Providing easier to take single combination pills available in India may improve adherence to treatment [46,47].

1.8 QUALITY OF LIFE ASSESSMENT

According to World Health Organization quality of life is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". Currently assessing quality of life in patients on a particular HIV treatment is considered as an important outcome of treatment, apart from clinical and cost outcomes. In many economic evaluations improvement in the health related quality of life is considered as one of the most important treatment benefits and they are measured using quality of life scales or questionnaires. Three are three main types of health related quality of life scales[48]: specific measures, general measures and preference-based measures. Specific measures are used to assess the quality of life related to a specific disease or medical condition or patient population. General measures are used to assess the overall quality of life and include multiple dimensions including physical, social and psychological parameters. Preference based measures are based on patients preferences for health states and provides numerical values for different health outcomes over time[49]. Preference based methods are widely used to measure the utility scores in cost effectiveness analysis. There are many preference based quality of life assessment questionnaires including European Quality of Life 5 dimensions questionnaires, Medical Outcomes Study 36 questionnaire, Medical Outcomes Study Short Form 6 dimensions questionnaire, Health Utility Index mark 2 classification system, Health Utility Index mark 3 classification system and Quality of Well-Being scoring formula that are used to

estimate the utility scores in cost effectiveness analysis[50]. The European quality of life 5 dimensions questionnaire and the medical outcomes study 36 questionnaires are generally preferred worldwide since these questionnaires have been standardized for different countries and for multiple disease conditions. For patients living with HIV these two questionnaires are widely used to estimate the quality of life utility index.

1.9 PROPENSITY SCORE ANALYSIS

In randomized controlled trials, patients are randomly assigned to comparison groups and do not differ on their baseline characteristics. The randomization procedure helps in computing unbiased estimates of average treatment effect. But in observational studies patients in the comparison groups often differ systematically based on their baseline characteristics and hence it is difficult to compute an unbiased estimates of average treatment effect[51,52]. Propensity score is a score computed from the study data that helps minimize the difference in baseline characteristics between the comparison groups[51]. Subjects with similar propensity scores will tend to have similar distribution of the observed baseline characteristics making the comparison groups similar conditional on the propensity scores, producing unbiased estimates of average treatment effect[52]. Propensity score analysis is based on two assumptions: the first assumption is that all the baseline variables that affect treatment assignment and outcome have been measured, i.e. the propensity score reduces the bias due to measured baseline variables only[51]. The second assumption is that every subject has a nonzero probability to be assigned to the comparison groups[51]. There are four different propensity score methods[53]: propensity score matching, stratification on propensity score, inverse probability of treatment weighting and covariate adjustment using propensity scores. In propensity score matching treatment effect is estimated by comparing propensity score matched sets of patients from the two comparison groups. In

stratification on propensity scores, patients are stratified into mutually exclusive quintiles of propensity scores and treatment effect is estimated by comparing each strata. Inverse probability of treatment weighting: this approach weights subjects by the inverse of their probability of receiving the treatment that the subject may have actually received. Individuals in one regimen receive an weight equal to $1/p_i$ and in other regimen receive a weight equal to $1/(1-p_i)$. The weights are then used in the weighted least squares regression model along with other predictor covariates to estimate treatment effect [54,55]. In the covariate adjusted propensity score method outcome variable are regressed on the comparison groups and propensity score. Propensity score matching and Inverse Probability of Treatment Weighting are considered to be more reliable than stratification and covariate adjustment[53,56,57]. We used Inverse Probability of Treatment Weighting in our study.

1.10 COST EFFECTIVENESS ANALYSIS

Cost effectiveness analysis compares the incremental costs (net resources used) and incremental health effects (net benefits achieved) for an intervention compared to an alternate intervention[49,58]. The incremental health effect can be any specific health effect of a program or an overall health improvement to a program[50]. In health economics the latter is widely used since it is a composite outcome which takes into account both patients preference and program specific outcomes. Quality adjusted life years are one of the common health outcomes recommended for cost effectiveness analysis, which includes both quality of life and life expectancy[49]. They incorporate both reduced morbidity and reduced mortality, and the preference people have for different outcomes in a single outcome measure[50]. Cost effectiveness analysis can be based on data already collected from randomized clinical trials and observational studies or from

pragmatic effectiveness clinical trials designed to collect clinical, economic, and quality of life outcomes in a real world setting[59-61].

Studies both from resource-sufficient and resource-limited settings have shown that a tenofovir-containing regimen is cost effective compared to a zidovudine-containing regimen. A study from Spain comparing these two regimens showed that the zidovudine-containing regimens are less expensive during the first three years, but with time both regimens had similar economic outcomes[62]. Another study also from Spain showed that patients on the tenofovir-containing regimen use fewer resources and have lower treatment costs than patients treated with the zidovudine-containing regimen[63]. A study from United States showed that the tenofovir-containing regimen is less costly and more effective than the zidovudine-containing regimen[64]. Similarly a study from sub-Saharan Africa showed the tenofovir-containing regimen was more cost effective than other regimens[65]. One study from India showed that the tenofovir-containing regimen was cost effective, but this was based on a simulation model using data collected from observational studies and clinical trials from both India and the United States[66]. To our knowledge there are no cost effectiveness analysis based on primary data collected from India comparing these two regimens. Studies from different settings have different outcomes and countries and regions have different requirements; for policy making, it is important to perform country specific cost effectiveness analysis.

1.11 COMPARATIVE EFFECTIVENESS STUDIES

Comparative effectiveness studies are conducted to generate and synthesize evidence that compares the benefits and harms of alternate methods for prevention, diagnoses, treatment and monitoring a disease or a clinical condition to make informed decisions and to utilize the available resources in the best possible way, to improve the health care[67]. Availability of

resources and the capacity to utilize them may differ between countries. Recommendations based on comparative effectiveness studies are not necessarily generalizable and often differ between countries[68,69]. Most of the studies included in decision making are from resource sufficient settings and the conclusions derived from these studies may not be appropriate in the resource limited settings[70]. Country specific comparative effectiveness studies are crucial for providing best possible health care to the patients.

This PhD thesis is a comparative effectiveness study which compares the current first line treatment regimen (zidovudine-containing regimen) to the alternative treatment regimen (tenofovir-containing regimen) for treatment of HIV in India. The objective of this PhD thesis is to compare the economic, clinical and quality of life outcomes in patients living with HIV on treatment with a zidovudine (along with lamivudine and nevirapine) or a tenofovir (along with emtricitabine and efavirenz) in an infectious disease clinic, at a private tertiary care hospital in southern India. To achieve this objective we conducted four different research projects:

Project 1: A prospective pilot project to document the toxicities that develop within six months of initiating the current first-line antiretroviral therapy, the zidovudine/stavudine containing regimen and the costs associated with treatment[71]. (Thuppal et al, JIAPAC)

Project 2: A retrospective data analysis comparing the toxicity and clinical outcomes in patients with HIV on zidovudine vs. tenofovir containing regimen for 36 months after treatment was initiated (Thuppal et al, TRSTMH).

Project 3: A randomized pragmatic clinical trial of zidovudine vs. tenofovir containing regimen in patients with HIV to compare the clinical outcomes, treatment costs and quality of life, with a follow-up of one year

Project 4: A cost effectiveness analysis of zidovudine vs. tenofovir containing regimen

METHODS AND RESULTS

2.1 Cost Estimation of First-Line Anti-Retroviral Therapy with Zidovudine/Stavudine as the Nucleoside Backbone in India: A Pilot Study

Methods

Study population: This study was conducted at the Government of India sponsored ART center at Christian Medical College (CMC), Vellore, Tamil Nadu, India. Adults above 18 years of age with a confirmed diagnosis of HIV, eligible for initiation of cART based on the National Aids Control Organization of India guidelines 2009, and willing to participate and follow-up for six months who provided written informed consent were enrolled. Participants requiring hospitalization at the time of initiation of cART, patients with active tuberculosis (TB) and those who were on treatment for TB, patients with diabetes or neurological impairment, pregnant and breast feeding women, and children were excluded. Patients were followed for six months and interviewed monthly to elicit incurred costs and other study related information. Treatment adherence was assessed using pill counts and patient interviews. The study was approved by the Institutional Review Board and Ethics Committee at Christian Medical College Vellore (IRB Min No. 7354 dated 08, December 2010).

Definition of toxicity: Drug related toxicity was assessed during all scheduled and unscheduled visits. Toxicity assessed in this study includes lactic acidosis (based on the levels of lactic acid > 2 mmol/L), peripheral neuropathy, severe anemia (defined as hemoglobin levels < 8 gram/dl) and neutropenia (defined as Absolute Neutrophils Count < 1000 cells per μl).

Cost calculation: Cost data were collected from patient interviews and medical bills. Collection drew on established methods for economic analysis in clinical practice[72]. Direct medical costs included costs attributable to pre-hospital visits, hospital visits, medication and diagnostics. Pre-

hospital visit costs are costs incurred during visits (direct and indirect costs) to any medical facility other than CMC for treatment between the scheduled visits. Hospital visit costs include professional charges, nursing charges, bed costs and any additional special costs associated with treatment. Drug costs include costs for cART (government procurement costs) and drugs for treating opportunistic infection and toxicity. Expenditures on radiological procedures and laboratory investigations were captured as diagnostic costs. Indirect costs for food, accommodation and transport for the patient and care giver were collected for every hospital visit. All costs were collected for inpatient, outpatient and emergency visits. Cost data were collected in Indian rupees from patient interviews and cash receipts. The unit costs for every intervention, all diagnostics, and all hospital charges are predetermined annually by the hospital administration, depending on local, geographical and economic factors.

Statistical Analysis: The pilot study included 50 participants to allow estimation of the mean cost with a 95% confidence interval of +/- 0.28 standard deviations. Analysis was done using statistical software SAS v.9.2 (32) (English).Means and proportions were computed to describe the baseline characteristics of individuals enrolled in the study. Socioeconomic status was assessed using the updated Kuppuswamy socio-economic scale[73]. For overall costs and individual cost components, the median and interquartile ranges (IQR) were computed. An exploratory analysis compared the baseline characteristics and costs for patients with and without toxicity.

Results

The study was conducted from February 2011 to November 2011. Fifty participants were enrolled into the study. Two participants were lost to follow-up. Among the remaining 48 participants, seven had other complications requiring hospitalization (pregnancy-1, adenocarcinoma-1 and tuberculosis within the first month of enrollment-5) and hence were withdrawn from the study. Forty-one participants successfully completed the six month follow-up and were included into the analysis. The mean age of enrolled participants was 37 years (standard deviation ± 9 years), with 21 (51%) males and 20 (49%) females. Of enrolled subjects, 35% were illiterate while the remaining 65% had formal education (Table 2). The population unemployment rate was 32%, and 76% of the employed people were unskilled laborers (Table 1). The mean weight at enrollment was 55 kg (standard deviation, ±15) with a baseline CD4 of 176 cells/ µl (standard deviation, ±105 cells/ µl). At the time of enrollment 22 (54%) of the patient were diagnosed with stage 1disease (Table 2). Based on baseline hemoglobin levels, zidovudine based regimen (zidovudine 300mg + lamivudine 150mg + Nevirapine 200mg) was started in 32 (78%) patients, while 9 (22%) were started on stavudine regimen (stavudine 30mg + lamivudine 150mg + nevirapine 200 mg). Treatment adherence exceeded 90%.

Table 2. Baseline demographic and clinical characteristics of participants

	All participants (n=41)	No toxicity (n=29)	Toxicity (n=12)	P value*
Demographic characteristics				
Age	37±9	36±8	42±12	0.139
Gender				0.431
Male n (%)	21 (51%)	16 (55%)	5 (42%)	
Female n (%)	20 (49%)	13 (45%)	7 (58%)	
Education n (%)				0.08
Illiterate	13 (35%)	8 (30%)	5 (50%)	
Middle School (class 6-8)	4 (11%)	4 (15%)	0%	
High School (class 9-12)	15 (40%)	13 (48%)	2 (20%)	
Graduate	5 (14%)	2 (7%)	3 (30%)	
Occupation n (%)				0.841
Unemployed	12 (32%)	8 (30%)	4 (40%)	
Unskilled	19 (51%)	14 (52%)	5 (50%)	
Semiskilled	2 (5%)	2 (7%)	0%	
Skilled	1 (3%)	1 (4%)	0%	
Clerical/shop/Farm	3 (8%)	2 (7%)	1 (10%)	
Socioeconomic Status n (%)				0.230
Lower	6 (16%)	4 (15%)	2 (20%)	
Upper lower	26 (70%)	19 (70%)	7 (70%)	
Lower middle	4 (11%)	4 (15%)	0%	
Upper middle	1 (3%)	0%	1 (10%)	
Clinical Characteristics				
CD4 at enrollment (cells/µl) (Mean±SD)	176±105	166±103	189±102	0.516
CD3 at enrollment (cells/µl)(Mean±SD)	1,130±668	1,170±624	1,038±719	0.608
Weight at enrollment (kg) (Mean±SD)	55±15	55±17	54±16	0.819
WHO disease stages n (%)				0.924
Stage 1	22(54%)	16(55%)	6(50%)	
Stage 2	2(5%)	1(3%)	1(8%)	
Stage 3	6(14%)	4(14%)	2(17%)	
Stage 4	11(27%)	8(28%)	3(25%)	

* Comparison between patients with and without toxicity

The median total direct costs for overall care and treatment of HIV over six months was INR 8,727 (US$ 168.40, 1US$= INR 52). Approximately 58% of the expenses were attributable to diagnostic tests, including radiological and laboratory investigations, followed by 33% of expenses attributable to drug costs, and 6% to hospital visit/admission costs. The median indirect cost over six months was INR 720 (US$ 14). Total costs for treatment were approximately INR

9,418 (US$ 181). Patient out of pocket expenditures for treatment were INR 7,157 (US$ 138). Total income earned during this six month period was INR 21,000 (US$ 404). Approximately 34% of the money earned during this six month period was spent on HIV treatment (Table 3).

Table 3 Median costs with inter-quartile range for treatment of HIV in India for a period of six months

	Overall Costs	No toxicity	Toxicity	P value
Diagnostic cost	5,045 (4,215-7,190)	4,915 (4,060-5,790)	7,653 (5,833-21,830)	0.005
Laboratory cost	4,845 (3995-6795)	4,695 (3740-8120)	6,748 (5360-20,738)	0.007
Radiology cost	175 (175-350)	175 (175-345)	513 (175-1210)	0.004
Drug cost	2,843 (2484-3338)	2,797 (2500-3032)	3,573 (2481-4406)	0.03
ART cost	2,502 (1851-2502)	2,502 (2190-2502)	2,189 (1634-2516)	0.69
Other medicine cost	548 (310-997)	295 (295-507)	1,180 (470-2112)	0.006
Hospital cost	470 (290-780)	410 (290-540)	1240 (500-12098)	0.006
Direct cost	8,727 (7548-10237)	7,920 (7172-9271)	11,422 (9598-40781)	<0.001
Indirect cost	720 (383-973)	580 (360-900)	810 (720-1050)	0.03
Total costs	9,418 (8110-11450)	8,680 (7628-10437)	12,045 (10658-41111)	<0.001
Total amount spent	7,157 (6132-13,100)	6,514 (5645-7935)	9,191 (8909-38,713)	<0.001
Income	21,000 (0-30000)	18,000 (0-30000)	22,500 (0-30000)	0.988

ART-Anti Retroviral Therapy; Costs: Indian Rupees INR, Median (IQR); Diagnostic cost: Money spent on laboratory tests and radiology investigation; Drug cost: Money spent for medicines other than ART and ART cost (ART is provided free of cost to all patients. The ART costs are the government procurement costs); Hospital cost: Include cost spent on registration for hospital visits (IP/OP/Casualty), consultant visit costs, medical records costs, billing costs and other special costs related to admission; Direct cost: Diagnostic cost+ Drug cost+ Hospital cost
Indirect cost per patient for the whole of 6 months: food cost+ accommodation cost +travel cost ; Total cost: Direct cost + Indirect cost; Total amount spent: Sum of all costs without ART costs

Of the 41 patients followed 12 (29.3%) had drug related side effects and required additional diagnostic tests for treatment. Eleven patients in the zidovudine regimen and one patient in the stavudine regimen had drug related toxicity. Five patients had severe anaemia requiring hospitalization and blood transfusion, four patients had anaemia treated with oral iron supplementation, two patients had skin rashes and one patient had both anaemia and skin rashes. All patients were switched from current regimen to less toxic regimens. Opportunistic infections were observed in 13 (31.7%) patients. Tuberculosis, pleural effusion, cryptosporidium infection,

eczema, diarrhoea, herpes infection and tuberculosis with lymphadenopathy was diagnosed in one patient each, while three patients had oral candida infection and three had lymphadenopathy.

Exploratory analysis comparing patients with and without toxicity showed that the two groups were similar with respect to all baseline characteristics (Table 2). Individual costs differed significantly between the two groups (Table 3). Patients with toxicity had to spend 44% more than those without toxicity for toxicity treatment and 56% more on laboratory and radiology tests. Patients with toxicity averaged 8.2 visits (standard deviation ± 2.0), approximately 50% more than the corresponding average of 5.5 visits for patients without toxicity (standard deviation ± 2.0). The number of outpatient referral visits to the infectious disease clinic was 40% more in patients with toxicity (7.6± 2.6 days) than for those without toxicity (5.4±2.3 days).

The baseline mean CD4 level of 176 cells/µl (standard deviation ± 105 cells/µl) increased significantly ($p<0.0001$) with treatment to 362 cells/µl (standard deviation ± 213 cells/µl) at the

Strengths and Limitations

To our knowledge, this study is the first study from India to estimate HIV care costs using individual level itemized costs for the current first line antiretroviral therapy. One of the limitations of this study is that the sample size of the study was small, however the study showed significant differences in costs between patients with and without adverse drug reactions. Secondly, the follow-up period was only for six months; however studies have shown that patients on the zidovudine containing regimen develop more adverse reactions during the first six months of treatment.

2.2 Toxicity and Clinical Outcomes in Patients with HIV on Zidovudine and Tenofovir Based Regimens: A Retrospective Cohort Study

Methods

Study population

The study population consisted of all adult ART naïve patients with a confirmed diagnosis of HIV infection, with a CD4 value < 200 cells/µl, who attended and initiated treatment at the Infectious Disease clinic at Christian Medical College, Vellore between January 2001 and June 2008. The free roll-out of government sponsored ART was initiated at this center in August 2008. Until that time, patients were required to buy their antiretroviral regimens; treatment was dependent on their ability to afford therapy. Approval for this study was obtained from the institutional review board at Christian Medical College.

ART regimens

The zidovudine containing regimen was a single combination pill including zidovudine 150mg, lamivudine 200mg and nevirapine 300mg given as two daily doses. The tenofovir containing regimen was a single combination pill including tenofovir 300mg, emtricitabine 200mg and efavirenz 600mg given as a single daily dose.

Data Collection

Data were extracted from electronic and paper based clinical records by a trained physician for a period of three years from the time of initiation of treatment (baseline). A second reviewer independently extracted data from a random ten percent sample of these records for quality assurance. Discrepancies were rectified by mutual consensus. Baseline demographic characteristics included patient's age at the time of clinic enrollment, sex, religion and

occupation. Baseline clinical details including baseline health conditions, weight, body mass index, CD4 count, clinical stage, time to treatment from the date of diagnosis of HIV, chronic health conditions and comorbidities and opportunistic infections were documented.

Outcome measures included drug specific ADRs, treatment change due to ADRs, opportunistic infections, treatment failure and requirement for inpatient admissions, change in CD4 counts, change in weight and change in body mass index. All the outcomes were documented based on the written record of the treating physician. Since the toxicity with each of the ART regimens being compared was specific to the drugs in the regimens, we included all ADRs, even if they occurred immediately after starting the treatment. When opportunistic infections occur immediately after the initiation of treatment, they may have been present sub-clinically before ART was begun; therefore we included only those opportunistic infections that developed more than three months after the initiation of ART for analysis. Treatment failure was diagnosed based on the immunologic parameters (steady decline in CD4: reduction in CD4 values compared to previous measurements, CD4 below the pretreatment value, CD4 less than 50% of the maximum documented value). Adherence was measured using pill counts and patient interviews. Other clinical conditions diagnosed during the follow-up period were also documented.

Statistical Analysis

Bivariate comparisons between zidovudine and tenofovir regimens were performed for all baseline characteristics. Two sample t-tests were used for continuous variables with normal distributions, non-parametric tests for continuous variables with non-normal distributions, and the chi-square test for categorical variables. The proportion of patients with treatment related ADRs, opportunistic infections and treatment failure in the zidovudine and tenofovir containing

regimens were compared. Change in CD4 count and body mass index from treatment initiation to the end of follow-up were compared between the two regimens.

Since our study was observational and ability to pay may have been associated with both selection of treatment regimen and other characteristics potentially influencing health, we used propensity score analysis to mitigate the potential confounding. In randomized controlled trials, patients are randomly assigned to comparison groups and do not differ on their baseline characteristics. But in observational studies patients in the comparison groups often differ systematically based on their baseline characteristics and hence it is difficult to compute an unbiased estimates of average treatment effect[51,52]. Propensity score is a score computed from the study data that helps minimize the difference in baseline characteristics between the comparison groups[51]. Subjects with similar propensity scores tend to have similar distribution of the observed baseline characteristics making the comparison groups similar conditional on the propensity scores, producing unbiased estimates of average treatment effect[52].

Propensity score estimation methods include logistic regression, classification trees, bagging and boosting, neural networks and recursive partitioning. A logistic regression method was used to estimate the propensity score in this study. The treatment status was regressed against all the baseline covariates measured before the treatment initiation and related to treatment and outcomes. The measured covariates included for estimating propensity scores for this study are age in years, weight in kilograms, delay in treatment initiation from the time of diagnosis in days and baseline CD4 counts as continuous variables and gender as male and female, occupation as employed and unemployed, WHO clinical stage at treatment including mild disease (stages 1 and 2) and severe disease (stages 3 and 4) and co-opportunistic infections as yes or no as categorical variables.

Treatment effect is estimated conditioned on the propensity scores. Two different treatment effects can be estimated using propensity score analysis: the average treatment effect on the treated and the average treatment effect in the population. Conditioning methods differ depending on the choice of treatment effect. Conditioning methods used to estimate the average treatment effect on the treated include: matching, stratification and weighting by odds. Conditioning methods used to estimate the average treatment effect in the population include matching, stratification, inverse probability of treatment weights and covariate adjustment.

For this study matching or stratification was not considered since the sample size was small and we expected to have small matched group or less number of patients in the different strata. To estimate the average treatment effect in the population we used the Inverse Probability of Treatment Weights (IPTW) conditioning method. This approach weights individuals by the inverse of their probability of receiving the treatment that the patient may have actually received. Individuals in one regimen receive an IPTW equal to $1/p_i$ and in other regimen receive a weight equal to $1/(1-p_i)$. The weights are then used in the weighted least squares regression model along with other predictor covariates [54,55]. One of the drawbacks of using IPTW is that the possibility of having extreme propensity scores leading to very large weights and affecting the overall treatment effect. Extreme weights can be adjusted by using different stabilizing techniques including: truncating the propensity scores, truncating the extreme weights and normalizing by dividing by the mean propensity score. In this study we used normalizing by dividing by the mean propensity score for the main analysis and stability was assessed by truncating both propensity scores and weights. As a sensitivity analysis we also performed covariate adjustment with propensity scores and compared the results with our main analysis. Univariate and multivariate comparison of the two regimens were performed using general linear model and

logistic regression procedures for continuous and categorical variables respectively. The treatment effect was estimated as adjusted differences in the mean for continuous variables and as adjusted odds ratios for categorical variables. Type III sum-of-squares analysis was performed to ensure that outcome differences are tested after adjusting for propensity score. We performed a multivariate analysis for important outcomes including ADR, opportunistic infections, weight and CD4 at end of follow-up. The purpose of the analysis was to assess the influence of various factors on the outcomes. All covariates, including baseline weight and CD4, age, occupation, gender, clinical stage at baseline and time to treatment were considered clinically significant and were included in the regression analysis. Since we hypothesized that patients with higher level of employment will tend to buy more expensive drugs, we also included an interaction term between treatment group and patient occupation. Since approximately 10% (24/221) of the data was missing, we did not use multiple imputation techniques in our analysis. All the analysis was done in SAS 9.2 (English) SAS Institute Inc., Cary, NC, USA.

Results

Study population characteristics

During the study period, 129 patients were started on the zidovudine containing regimen and 92 patients on the tenofovir containing regimen. The mean age was 40 (SD-8.7) years and 71% of the subjects were male. The median (interquartile range) weight and CD4 count at the start of treatment were 60 kg (50-68) and 159 cells/ µl (63-228) respectively, and the values were comparable between regimens (Table 4). Patients on the tenofovir containing regimen had more professional or semi- professional jobs, were older, had more severe infections and there was less

time between diagnosis and initiation of treatment than patients on the zidovudine containing regimen (Table 4).

Table 4. Baseline characteristics of the study population

Variable	Zidovudine containing regimen (AZT)	Tenofovir containing regimen (TDF)	p-value
Gender[a] n (%) Male	92/129 (71.3)	65/92 (70.6)	0.91
Age in years[b] Median (IQR)	37 (33-41)	40 (34-46)	<0.001
Occupation[a] n (%)			<0.001
Professional	6/129 (4.7)	11/92 (12)	
Semi-Professional	12/129 (9.3)	15/92 (16.5)	
Clerical	36/129 (28.1)	25/92 (27.5)	
Skilled worker	15/129 (11.7)	7/92 (7.7)	
Unskilled worker	32/129 (25)	5/92 (5.5)	
Unemployed	27/129 (21.1)	28/92 (30.8)	
WHO clinical stage before treatment[a] n (%)			0.03
Stage 1	42/129 (32.5)	22/92 (23.9)	
Stage 2	21/129 (16.3)	6/92 (6.5)	
Stage 3	19/129 (14.7)	16/92 (17.4)	
Stage 4	47/129 (36.4)	48/92 (52.1)	
Co-Opportunistic Infection[a] n (%)	43/129 (33.3)	39/92 (42.4)	0.16
Median delay in treatment from the time of diagnosis in days[b] (IQR)	118 (29-779)	36 (11-49)	<0.01
Median BMI at the start of treatment in kg/m^2 [b](IQR)	22.3 (19.3-24.6)	21.1 (19- 24.7)	0.54
Median Cd4 at the start of treatment in cells/µl[b] (IQR)	168 (72-228)	134 (54-227)	0.21

AZT-Zidovudine; TDF- Tenofovir

[a]Chi-square test for comparing difference in proportions; [b]Non-parametric test (Kruskal-Wallis Test) for comparing difference in median

BMI- Body Mass Index; IQR- Inter Quartile Range; NS- Non Significant P-values; WHO- Word Health Organization

Co-Opportunistic Infection: patients who had opportunistic infections at the time of initiation of therapy

Outcome measures

There was a significant difference between the zidovudine (47%) and tenofovir (11%) containing regimens in the proportion of patients who experienced ADRs (p value- <0.01) (Table 5). After adjusting for propensity score, patients on the zidovudine containing regimen were 8.7 times (95% CI- 4.03-18.88) more likely to experience an ADR compared to patients on the tenofovir containing regimen (Table 5). When adjusting for the propensity score and other baseline variables, the likelihood of the patients receiving the zidovudine containing regimen developing an ADR increased to 12.6 times (95% CI-5.2-30.7) the likelihood of patients receiving the tenofovir containing regimen. In the multivariate regression model, none of the other variables had significant influence on ADR

Table 5. Study outcomes with and without Propensity Score (PS) adjustment

Variables	Without PS adjustment			With PS adjustment		
	Zidovudine containing regimen (AZT) n (%)	Tenofovir containing regimen (TDF) n (%)	P value	OR[a]	95% Confidence Interval	P value
Adverse drug reaction (n=AZT-129, TDF-92)	61/129 (47.3)	10/92 (10.9)	<0.001	8.725	4.032-18.883	<0.001
OI after 3 months (n=AZT-129, TDF-92)	26/129 (20.1)	17/92 (18.5)	0.75	1.182	0.591-2.364	0.63
In-Patient admissions (n=AZT-129, TDF-92)	30/129 (23.3)	18/92 (20)	0.51	1.006	0.52-1.947	0.98
	Zidovudine containing regimen Mean (SD)	Tenofovir containing regimen Mean (SD)	P value	Zidovudine containing regimen Mean (SD)	Tenofovir containing regimen Mean (SD)	P value[b]
Change in BMI[c] (n, AZT-90, TDF-57)	1.8 (2.5)	3.6 (3)	<0.01	1.9 (2.3)	3.7 (3.1)	<0.01
Change in CD4[c]	359 (220)	388 (198)	0.2	358 (212)	358 (208)	0.99

OI- Opportunistic Infections; AZT-Zidovudine; TDF-Tenofovir

[a]PS adjusted odds ratio, reference group for comparison is tenofovir containing regimen; [b]PS adjusted comparison of means

[c]Change in Body Mass Index (BMI) in kg/m^2 and CD4 cells/µl between treatment initiation and end of follow-up

NS-Non Significant p-values; SD-Standard Deviation;

Zidovudine was associated with anaemia (47%) and anaemia was the most frequently diagnosed ADR, followed by the nevirapine associated skin reactions (12%). Approximately 60% of the patients with ADRs required a drug change; approximately half of these were due to zidovudine associated anemia (Table 6). The proportion of patients requiring regimen change due to ADRs with the zidovudine containing regimen was 36% as compared to 3% with the tenofovir containing regimen. Stavudine was replaced in place of zidovudine in 26 (36%) of patients with zidovudine associated anemia; of these, 11(42%) had an additional ADR due to stavudine requiring a drug change back to zidovudine. Of the 13 patients with nevirapine associated ADRs, 12 (92%) patients were switched to efavirenz, while of the 5 patients with tenofovir associated ADRs, 3 (60%) patients were switched to abacavir (Table 6).

Table 6. Adverse drug reactions diagnosed and treatment change

Adverse Drug Reaction	Drug	Number of cases (%)[a]	Required change of regimen (%)[b]
Anemia	Zidovudine	37 (47)	26 (53)
Pancytopenia	Zidovudine	3 (4)	3 (6)
Skin Rash	Nevirapine	9 (12)	8 (16)
Hepatitis	Nevirapine	4 (4)	4 (8)
GI disturbances		7 (9)	0
Lypodystrophy	Stavudine	5 (6)	2 (4)
Peripheral Neuropathy	Stavudine	3 (4)	0
Lactic Acidosis	Stavudine	3 (4)	3 (6)
Renal Tubular Acidosis	Tenofovir	2 (3)	2 (4)
Hypophosphatemia	Tenofovir	3 (4)	1 (2)
CNS Disturbances	Efavirenz	2 (3)	0
Total		78	49

[a]Percentage out of total number of cases with ADR; [b]Percentage out of total number of cases requiring change of regimen; GI-Gastro Intestinal; CNS-Central Nervous System

The proportion of patients experiencing opportunistic infections more than three months after initiation of ART was the same in the zidovudine containing (20%) and tenofovir containing (19%) regimen (Table 5). After adjusting for propensity score, however patients receiving the

zidovudine containing regimen developed opportunistic infections 1.2 times (95% CI: 0.591-2.364, p value: 0.63) more often than patients on the tenofovir containing regimen. After adjusting for propensity score and other baseline variables this increased further to 1.5 times (95% CI: 0.67-3.2, p value: 0.34), than seen in the tenofovir group. None of the other baseline variables had a significant influence on opportunistic infections. Bacterial skin infections (31%) were the most common opportunistic infection followed by candidal infections (13%) (Table 7).

Table 7. Opportunistic Infections diagnosed during the study period

Opportunistic Infections	Zidovudine containing regimen	Tenofovir containing regimen	Total (%)[a]
Pneumocystis Pneumonia	2	0	2 (4)
Candidal Infection	6	0	6 (13)
Chronic Diarrhea	3	3	6 (13)
Herpes Zoster	3	3	6 (13)
Herpes Simplex	3	0	3 (7)
Bacterial skin infections	6	8	14 (31)
Nonalcoholic chronic liver disease	1	0	1 (2)
Pulpitis	1	0	1 (2)
CMV retinitis	1	0	1 (2)
Tuberculosis	3	2	5 (11)
Total	28	17	45

[a]Percentage of patients out of total cases of Opportunistic Infections; CMV- Cytomegalovirus

The comparison of both regimens to determine the proportion of patients who had opportunistic infections at the time of initiation of therapy (co-OI) found no difference between the two (Table4). But after adjustment for propensity score, the patients in the zidovudine containing regimen were 40% less likely to have a co-OI than the patients in the tenofovir containing group (Odds Ratio-0.61, 95% CI- 0.35-1.06; p-value-0.08). Similar results were seen while comparing opportunistic infections during the first 3 months of treatment (Odds Ratio-0.6, 95% CI- 0.3-1.23) and all opportunistic infections together (Odds Ratio-0.5, 95% CI- 0.28-0.88).

Body Mass Index increased in patients on both the regimens, the change in body mass index from treatment initiation to the end of follow-up in patients on the tenofovir containing regimen was twice that seen in the patients in the zidovudine containing regimen. This was true whether or not propensity score adjustment was done (Table 5). The change in CD4 count from treatment initiation to the end of follow-up did not differ between those on either regimen. Again, this was true whether or not propensity score adjustment was done (Table 5). When adjusted for other covariates, it was patients with severe disease (WHO clinical stages 3 and 4) and young patients who gained more weight and had increased body mass index. Compared to male patients female patients had a significant increase in CD4 counts. Four patients taking the zidovudine containing regimen had treatment failure, compared to none who were taking the tenofovir containing regimen. The adherence to treatment was more than 95% in both the regimens and did not differ with and without propensity score adjustment. The number of inpatient admissions was similar between the treatment regimens and did not differ with or without PS adjustment (Table 5). No patients died or were lost to follow-up over the course of the study.

The outcome measures with normalizing with mean PS was consistent with both stability assessment and sensitivity analysis.

Strengths and Limitations

One of the strengths of this study is the use of propensity score adjustment to account for the differences in the baseline characteristics between the drug regimens. To our knowledge this is the first study to compare these two drug regimens from India. As any other observational study our study also has certain limitations and bias. Though propensity score adjustment accounts for measured confounders, it does not account for unmeasured confounders such as substance abuse

(alcohol) and sexual behavior. Outcomes were ascertained based on the written record of the treating physician. As a non-randomized, retrospective study we cannot eliminate the bias of providers in prescribing the tenofovir or zidovudine based regimen for a particular patient; nor could we control for the ability of a particular patient to be able to afford the tenofovir containing regimen rather than the zidovudine containing regimen. The regimens also differed in composition other than AZT and TDF as well as in requirement for once or twice daily dosage.

2.3 Clinical Outcomes, Treatment Costs, and Quality of Life in Patients with HIV on Zidovudine and Tenofovir Containing Regimens in India: A Pragmatic Randomized Clinical Trial

Materials and Methods

Objectives and hypothesis

The objective of this randomized controlled trial was to compare the rate of ADR along with other clinical outcomes including opportunistic infections (OI), treatment failure, treatment adherence, change in nutritional status, change in CD4 count, QoL and treatment costs over a period of one year for patients randomized to either the zidovudine- or the tenofovir-containing regimen. We hypothesized that patients receiving the tenofovir-containing regimen would have fewer ADR and exhibit greater antiretroviral therapy adherence. Better adherence would in turn improve CD4 counts and rates of viral suppression, reduce the frequency of OI and result in better QoL compared with patients receiving the zidovudine-containing regimen. We also hypothesize that fewer ADR and OI will reduce the overall treatment costs.

Drug regimens

The zidovudine-containing regimen was a single combination pill including zidovudine 150mg, lamivudine 200mg and nevirapine 300mg given as two daily doses. The tenofovir-containing regimen was a single combination pill including tenofovir 300mg, emtricitabine 200mg and

efavirenz 600mg given as a single daily dose. The drugs were supplied by Emcure Pharmaceuticals Limited.

Study participants

This study was conducted at the Infectious Disease Clinic at the Christian Medical College and Hospital (CMC), a tertiary care private hospital, in Vellore, Southern India. The trial enrolled all treatment naïve adults 18 years and older with a confirmed diagnosis of HIV, eligible for antiretroviral therapy as per the recommendations of the National AIDS Control Organization, Government of India.[1] According to the current Government of India recommendations treatment is initiated when the CD4 cell count falls below 350cells/µl or in individuals with severe or advanced disease irrespective of CD4 count. We excluded patients requiring hospitalization at the time of treatment initiation, patients with hemoglobin levels less than 8 mg/dl, patients with active OI, patients with co-morbidities including renal failure and neurological impairment, pregnant and breast feeding women, and children less than 18 years old. The study was approved by the Institutional Review Board at CMC, India and Tufts Medical Center, Boston, USA. The study was registered with clinicaltrials.gov, NCT01694017. Informed consent was obtained from all the participants. This manuscript was prepared based on the CONSORT extension for reporting Pragmatic Trials guidelines.[74]

Sample size

The sample size was calculated based on proportion with ADR after one year of treatment, the primary study outcome. Assuming an ADR of 28.5% for patients on zidovudine-containing regimen[25,71] and 2% for patients on tenofovir-containing regimen,[28,29,75] we required a sample size of 30 patients per arm to detect a statistically significant difference between the two

regimens with 80% power and alpha of 0.05 (z-test, assuming equal sample size). Assuming a 10% loss to follow-up, we derived a final sample size of 35 patients for each treatment regimen.

Randomization and Blinding

Study sampling was performed by consecutive recruitment and enrollment. We screened each potential participant using our pre-defined inclusion/exclusion criteria and provided information about the study. Upon consenting to participate, patients were randomized based on codes generated from random number tables using a computerized program. This study was not blinded since the study funding was not sufficient to obtain blinded antiretroviral drugs.

Study Outcomes

Demographic and clinical characteristics including age, gender, socioeconomic status as described by education, occupation and household monthly income, HIV disease stage and coexisting health conditions were collected at the time of recruitment. Socioeconomic status was assessed using the updated Kuppuswamy socio-economic scale.[76]

The proportion of patients experiencing an ADR was the primary outcome. Other outcomes included toxicity associated treatment change, OI and treatment failure, change in nutritional status, treatment adherence, treatment costs over the one year study period and QoL.

We recorded any toxicity experienced following treatment initiation and all OIs diagnosed during follow-up. To assess for ADR, clinical examination for symptoms and blood tests for safety labs were performed after 15 days of initiation of antiretroviral therapy. Thereafter clinical assessment was performed during the monthly follow-up visits and blood tests were obtained every six months. The ADRs included in the study are drug specific and have been characterized by World Health Organization[77]. Adverse drug reactions associated with the antiretroviral drugs include: zidovudine induced anemia (hemoglobin levels < 8 gram per cent)

and neutropenia (absolute neutrophils Count < 1000 cells per µl), nevirapine induced hepatotoxicity (assessed by the elevated levels of alanine aminotransferase (7-55 units per liter), and aspartate aminotransferase (10-40 units per liter)) , skin rash (clinical assessment) and hypersensitivity reactions, tenofovir induced renal tubular acidosis (based on creatinine levels 0.4-1.4 milligram per deciliter and serum urea 15 to 50 mg/dL), lactic acidosis (lactic acid > 2 mmol/L) and bone mineral density (based on serum calcium 8.4 - 10.2 mEq/dl and serum phosphorus 3.0 - 4.5 mg/dL), and efavirenz induced abnormal dreams, depression or mental confusion and male gynecomastia (clinical assessment).

Treatment failure was defined by immunologic parameters (Steady decline in CD4: steady decline in CD4 values compared to previous measurements, CD4 below the pretreatment value, CD4 less than 50% of the maximum documented value.) and virologic parameters (Any viremia exceeding 1000 copies/µl was considered as treatment failure and any viral load value < 40 copies/µl were considered optimal viral suppression.).[1] Nutritional status was assessed by comparing the change in body mass index (BMI) between treatment initiation and end of follow-up between the two regimens. Antiretroviral therapy was dispensed on a monthly basis and data on adherence were collected during each visit. Adherence was assessed using pill counts and patient interviews at monthly pill pick-ups. Adherence was calculated as the number of pills consumed compared to the total number of pills dispensed during each monthly visit; mean adherence was calculated for each patient. All patients were counseled to encourage strict drug adherence and timely intake of tablets during monthly visits and were educated about the potential for complications if they did not adhere to treatment.

Any unscheduled visit to the study hospital, or to any other facility during the course of treatment, was also documented. Blood samples for hemoglobin, alanine aminotransferase

(ALT), aspartate aminotransferase (AST) and creatinine levels were collected at treatment initiation and at the end of follow-up. All laboratory tests were conducted in the hospital laboratories using standardized protocols.

Cost data were based on patient interviews and medical bills. Collection of these data drew on established methods for economic analysis in clinical practice.[72] Direct medical costs included costs attributable to pre-hospital visits, hospital visits, medication and diagnostics. Pre-hospital visit costs included costs incurred during visits to any medical facility including CMC for treatment between the scheduled study/clinic visits. Hospital visit costs include professional charges, nursing charges, bed costs and any additional special costs associated with treatment. Drug costs included costs for antiretroviral therapy and the cost of other drugs required for treating opportunistic infection or toxicity. Expenditures on radiological procedures and laboratory investigations were recorded as diagnostic costs. Indirect costs for food, accommodation and transport for the patient and care giver were collected for every clinic and hospital visit. The direct and indirect costs were collected for inpatient, outpatient and emergency visits. Cost data were collected in Indian rupees from patient interviews and review of cash receipts. The unit costs for every intervention, diagnostic, and hospital charges were determined annually by the hospital administration by standardized cost accounting

Health related QoL was assessed using the European Quality of Life -5-Dimensions (EQ5D) and Medical Outcomes Study 36 (MOS36) scoring systems. Both scoring systems have been standardized for patients with HIV and have been administered in resource limited settings including India. EQ5D scores were converted to health utility measures using EQ-5D-5L Index Value Calculator, Version 1.0.[78,79] MOS 36 was converted to Short Form- 6 Dimensions (SF-6D) using standard protocols and the results were used to calculate health utility values.[80,81]

Both the questionnaires were administered quarterly and each subject's mean health utility value was calculated over a period of one year.

Statistical Analysis

Intent to treat analysis was performed to compare the treatment effects between the two regimens. Differences in clinical outcomes were compared using two sample t-tests for normally distributed continuous variables, and the Wilcoxon rank sum test for continuous variables with non-normal distributions, and the chi-square test for categorical variables. The proportion of patients experiencing the ADR, requiring regimen change due to an ADR and the rates of development of OI during follow-up were compared between the two drug regimens using the chi-square test. Mean change in BMI and CD4 from treatment initiation to end of follow-up, and mean adherence to treatment were compared using two sample t-tests. Overall costs and individual cost components were summarized in terms of their medians and inter quartile ranges and compared using the Wilcoxon rank sum test. Two sample t-tests were used to compare the mean yearly QoL index. All the analysis was done in SAS 9.2 (English) SAS Institute Inc., Cary, NC, USA.

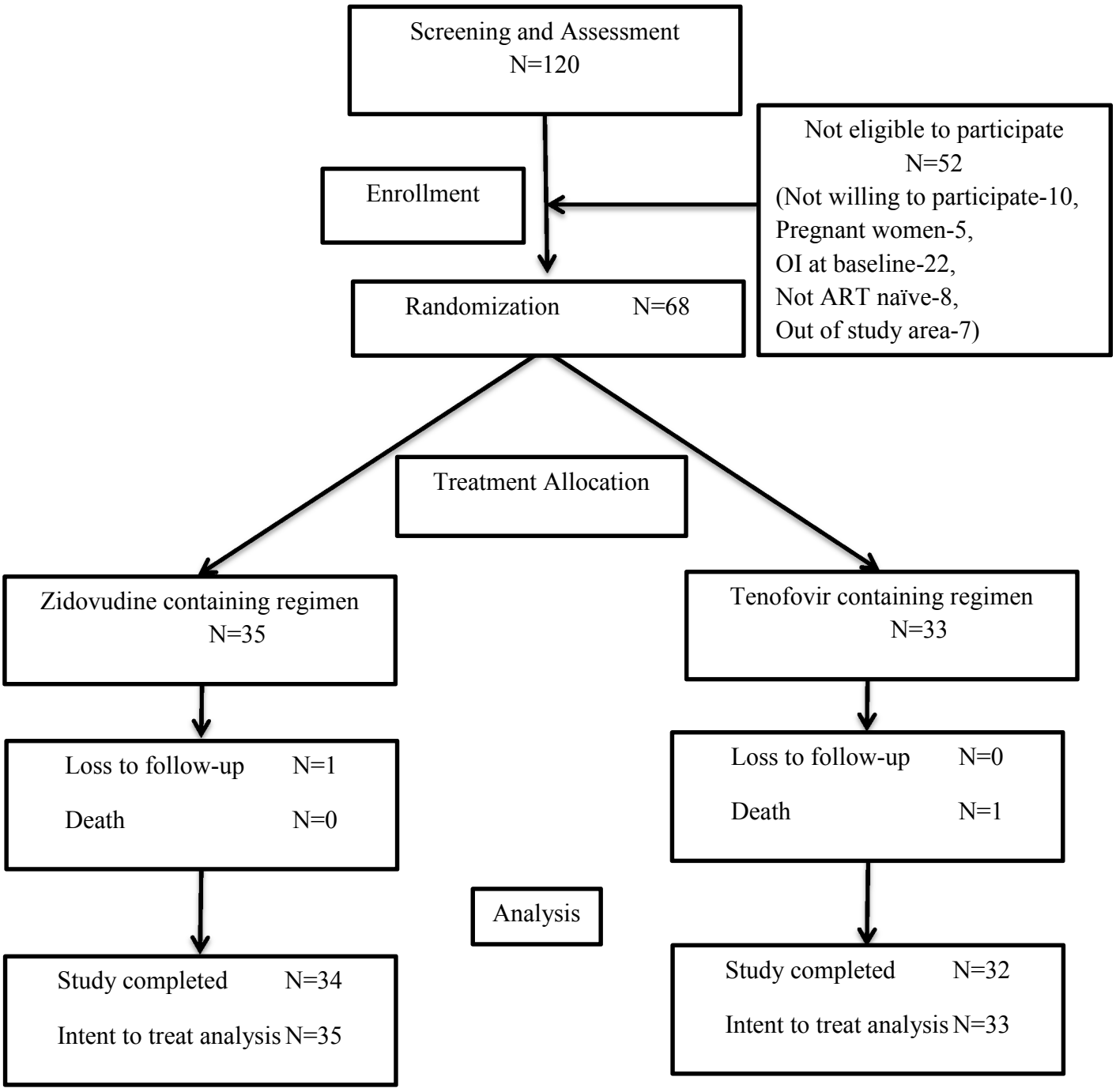
Results

Enrollment and follow-up

This trial was conducted between July, 2012 and August, 2014. Of the 120 participants screened, 35 and 33 were randomized to zidovudine and tenofovir-containing regimen, respectively. One patient in the zidovudine group was lost to follow-up. This patient developed a skin rash due to nevirapine and refused to continue treatment after six months of follow-up. One patient receiving the tenofovir-containing regimen died of an unrelated cause after six months follow-up. Outcome data, including ADRs, OIs, toxicity associated treatment change, treatment adherence, treatment

costs and QoL were included in the intent to treat analysis. All other patients completed the study as scheduled (Figure 1).

Figure 1 Flow diagram of participant enrollment and follow-up



ART- antiretroviral therapy; OI-opportunistic Infection

Baseline demographic characteristics:

The average age of participants was 38 years (standard deviation, SD: 7.1) and 44% were men. Eight four percent were married, 68% were employed, and 90% had some formal education. No study participants were in the high socioeconomic category; 31% were of middle socioeconomic status and 69% were of low socioeconomic status. None of the participants had severe disease (stage 4) and 84% had asymptomatic infection (stage 1) at recruitment. There was no difference in the baseline characteristics between the participants on the two regimens (Table 8).

Table 8: Baseline demographic and clinical characteristics of patients living with HIV on treatment with zidovudine and tenofovir containing regimen

	zidovudine containing regimen (n=35)	tenofovir containing regimen (n=33)
Age (years) mean (SD)[a]	37.7 (7.05)	37.9 (7.37)
Male n (%)[b]	15 (43)	15 (45)
Marital Status n (%)[b]		
Married	31 (89)	26 (79)
Widowed	4 (11)	6 (18)
Separated	0	1 (3)
Education n (%)[b]		
Graduate or post graduate	5 (14)	6 (18)
Intermediate or post high school diploma	1 (3)	6 (18)
High school certificate	16 (46)	12 (36)
Middle school certificate	3 (9)	5 (15)
Primary school certificate	6 (17)	2 (6)
Illiterate	4 (11)	2 (6)
Income in Indian Rupees n (%)[b]		
>19575	1 (3)	2 (6)
9788-19574	2 (6)	2 (6)
7323-9787	2 (6)	7 (21)
4894-7322	10 (29)	3 (9)
2936-4893	5 (14)	3 (9)
980-2935	6 (17)	9 (27)
<979	9 (26)	7 (21)
Occupation n (%)[b]		
Professional	2 (6)	1 (3)
Semi-professional	0	1 (3)
Clerical, shop-owner, farmer	1 (3)	0
Skilled worker	2 (6)	7 (21)
Semi-skilled worker	6 (17)	11 (33)
Unskilled worker	10 (29)	5 (15)
Unemployed	14 (40)	8 (24)

Socioeconomic status n (%)[b]		
Upper middle	2 (6)	5 (15)
Middle lower middle	7 (20)	7 (21)
Lower upper lower	24 (69)	20 (61)
Lower	2 (6)	1 (3)
Clinical Stage n (%)[b]		
I	30 (86)	27 (82)
II	4 (11)	1 (3)
III	1 (3)	5 (15)
CD4 count[a]	222 (81)	207 (110)
BMI (mean (SD))[a]	22 (3.4)	23 (4)

[a]Two sample ttest; [b] chi-square test; BMI- Body Mass Index; SD- Standard Deviation

Clinical outcomes

Adverse Drug Reactions: The proportion of patients experiencing an ADR was significantly higher in patients randomized to the zidovudine-containing regimen (89%) than those in the tenofovir arm (45%) (P- value : < 0.01). Regimen change due to ADR was required in 35% and 7% of patients receiving the zidovudine and tenofovir-containing regimen, respectively (p-value: < 0.01) (Table 9).

Table 9: Clinical Outcomes Diagnosed and Quality of Life measured in patients living with HIV on treatment with zidovudine and tenofovir containing regimen

	Zidovudine containing regimen(n=35)	Tenofovir containing regimen(n=33)	P value
Adverse Drug Reactions n (%)	31 (89)	15 (45)	<0.01
Regimen Change due to adverse drug reactions	11 (31)	2 (6)	<0.01
Opportunistic Infection n (%)	16 (46)	10 (31)	0.22
Other morbidities n (%)	12 (34)	12 (37)	0.78
In-patient visit n (%)	6 (17)	3 (9)	0.35
Change in BMI (kg/cm^2) mean (SD)	0.67 (2.75)	0.3 (1.4)	0.48
Change in CD4 (cells/µl) mean (SD)	208 (132)	246 (172)	0.32
Adherence (%) mean (SD)	99.34 (1.7)	99.56 (1.2)	0.55
SF6D	0.869 (0.843-0.891)	0.857 (0.832-0.898)	0.52
EQ5D	0.949 (0.881-1.0)	0.942 (0.908-0.969)	0.95

BMI- Body Mass Index; EQ5D- European Quality of Life 5 Dimensions; SD- Standard Deviation; SF6D- Medical Outcomes Study Short Form 6 Dimensions;

In the zidovudine arm, zidovudine induced anemia (49%) and gastrointestinal disturbances (40%) were the most frequently diagnosed ADR, while efavirenz induced dizziness (30%) was the most frequently diagnosed ADR among the patients receiving the tenofovir-containing regimen (Table 10). Regimen change was required in 88% of patients with skin rash and 29% of patients with anemia.

Table 10 Adverse drug reactions diagnosed during the study period

Adverse Drug Reaction	Zidovudine containing regimen (n=35) n (%)	Tenofovir containing regimen (n=33) n (%)
Anemia	17 (49)	1 (3)
Skin Rash	4 (11)	4 (12)
Hepatitis	7 (20)	0
Gastro Intestinal discomfort	14 (40)	3 (9)
Dizziness	2 (6)	10 (30)
Headache	0	1 (3)
Insomnia	0	1 (3)
Impaired concentration	0	1 (3)
Renal impairment	0	1 (3)

Opportunistic Infections: The proportion of patients experiencing an OI on the zidovudine-containing regimen (46%) was greater than patients on the tenofovir-containing regimen (31%), although this difference was not statistically significant (P value: 0.22) (Table 2). Candidal infections (20%) and bacterial respiratory infections (14%) were the most common OIs observed among patients receiving zidovudine-containing regimen, while diarrhea (15%) was the most common OI observed among patients receiving the tenofovir-containing regimen (Table 4).

Table 11 Opportunistic Infections diagnosed during the study period

Opportunistic Infections	Zidovudine containing regimen (n=35) n (%)	Tenofovir containing regimen (n=33) n (%)
Pneumocystis Pneumonia	1 (3)	0
Candidal Infection	7 (20)	0
Infectious Diarrhea	1 (3)	5 (15)
Herpes Zoster	3 (9)	3 (9)
Herpes Simplex	4 (12)	2 (6)
Bacterial skin infections	0	1 (3)
Bacterial Enteric Infection	1 (3)	1 (3)
Hepatitis C	0	1 (3)
Cryptococcal infection	0	1 (3)
Tuberculosis	2 (6)	0
Bacterial Respiratory Infection	5 (14)	0

Immunologic and Virologic Parameters: At baseline, the mean CD4 cell count was below 350 cells/ µl (Criterion for starting antiretroviral therapy as per National AIDS Control Organization recommendations.) in both the treatment groups (Table 1). The CD4 count did not differ significantly between the two groups at baseline or at the end of follow-up (Supplementary Table 2). The CD4 count increased with treatment in both study arms, but the incremental gain tended to be higher among patients receiving tenofovir-containing regimen (246 cells/µl, Standard

Deviation (SD)-172) than that in patients receiving the zidovudine-containing regimen (208 cells/µl, SD-132). However, this difference did not achieve statistical significance (p-value: 0.32) (Table 2). Treatment failure occurred in five patients, three in the zidovudine group and two in the tenofovir group. All other patients achieved optimal viral suppression, below the limit of detection of the assay (viral load < 40 cells/µl). One patient in each group experienced both immunologic and virologic failure.

Other Clinical Outcome: At recruitment and at the end of follow-up, patients in both treatment groups had similar BMI which were within normal limits (Table 1). The change in BMI between treatment initiation and the end of 12 months of follow-up did not differ between the two drug regimens (Table 2). Overall adherence to treatment was 99.5% and was similar in the two treatment regimens. There was no difference between the two groups in terms of the proportion of patients requiring inpatient admission during the course of treatment (Table 2). All lab parameters, including serum hemoglobin, ALT, AST and creatinine were within normal limits at the time of treatment initiation and at the end of follow-up and did not differ between the two treatment groups (Table 5).

Table 12: Laboratory Investigations at baseline and end of follow-up

	At baseline mean (SD)			At End of follow-up mean (SD)		
	Zidovudine containing regimen (n=34)	Tenofovir containing regimen (n=33)	p-value	Zidovudine containing regimen (n=29)	Tenofovir containing regimen (n=31)	p-value
Serum Hemoglobin (g/dl)	12.9 (2.2)	12.7 (1.3)	0.56	12.7 (1.4)	13 (1.3)	0.51
Serum Creatinine (mg/dL)	0.96 (0.15)	0.98 (0.18)	0.61	0.75 (0.2)	0.72 (0.3)	0.54
Blood ALT (U/L)	24.2 (11.7)	26.6 (11.3)	0.39	22.1 (7.5)	23.5 (9.8)	0.5
Blood AST (U/L)	18.9 (11.9)	21 (13.4)	0.51	22.2 (9.9)	20.7 (11.1)	0.6
CD4 count Cells/µl	222 (81)	207 (110)	0.08	420 (161)	451 (220)	0.5

Two sample ttest was used to compare the values between regimens; ALT- Alanine Aminotransferase; AST- Aspartate Aminotransferase; SD- Standard Deviation

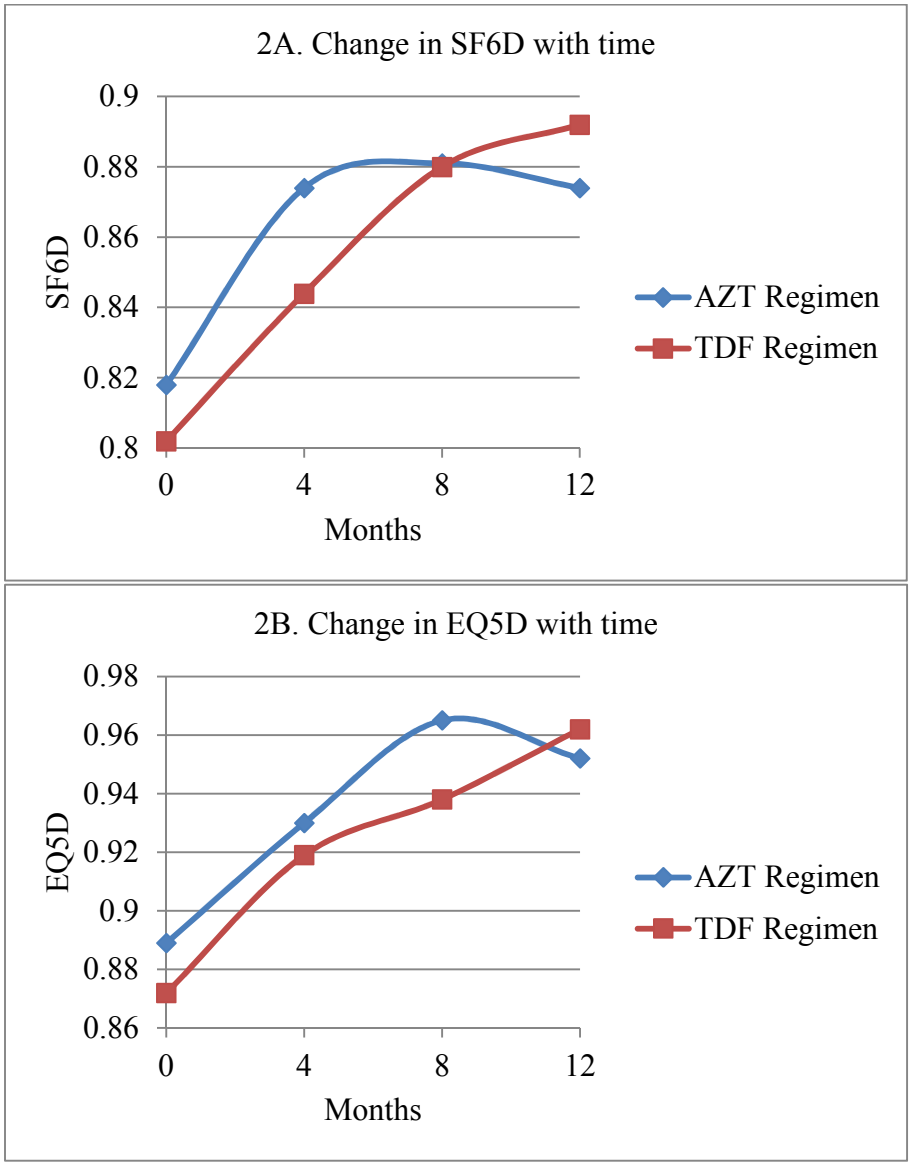
One study participant in the tenofovir arm died following approximately six months of follow-up due to end stage B cell leukemia. This patient was apparently healthy until one month before death and was diagnosed only few weeks prior to her death. Possibly, the patient had the disease even before the treatment was started. One patient in the zidovudine group was lost to follow-up. This patient developed a skin rash due to nevirapine and refused to continue treatment after six months of follow-up.

Quality of Life

QoL measures (EQ5D and SF6D) for patients in both treatment groups were similar at the end of follow-up (Table 2). Although the mean QoL did not differ significantly between the two treatment groups, it increased steadily over time among patients receiving the tenofovir-

containing regimen through the one year treatment period, whereas among patients receiving zidovudine-containing regimen, it increased during the first few months of treatment and then declined towards the end of the one-year treatment period (Figure 2).

Figure 2 Change in QoL over one year period on treatment with zidovudine and tenofovir containing regimen



AZT- Zidovudine Containing Regimen; EQ5D- European Quality of Life 5 Dimensions; SF6D- Medical Outcomes Study Short Form 6 Dimensions; TDF- Tenofovir Containing Regimen

Treatment costs

Overall median costs (expressed in Indian Rupees) for the zidovudine and tenofovir-containing regimen were 14,518 (Inter Quartile Range (IQR): 12,422-19,910) and 15,345 (IQR: 12,601-18,537), respectively (P value: 0.864). Diagnostic costs, cost of other medications, hospital costs, direct costs, indirect costs and total costs were similar between the two treatment regimens when antiretroviral therapy costs were not included. The antiretroviral therapy drug cost of tenofovir-containing regimen is more expensive than the zidovudine-containing regimen. And as expected, calculated costs for the two regimes differed significantly, when the antiretroviral therapy drug costs were included along with direct costs and other costs (Table 13).

Table 13: Median costs with inter-quartile range for one year period

	zidovudine containing regimen	tenofovir containing regimen	P value
Diagnostic cost	10810 (8375-12625)	10624 (8840-12125)	0.9
Laboratory cost	10660 (8225-12475)	10390 (8690-11825)	0.97
Radiology cost	150 (150-340)	150 (150-300)	0.86
Drug cost	15434 (15007-28468)	47488 (46987-47780)	<0.01
ART cost	14400(14400-27730)	46800 (46800)	<0.01
Other medicine cost	729 (602-1520)	688 (187-980)	0.07
Hospital cost	260 (195-615)	325 (260-510)	0.69
Direct cost with ART	28432 (24349-51110)	58881 (56617-60114)	<0.01
Direct cost without ART	12381 (9949-16321)	12081 (9817-13314)	0.52
Indirect cost	2240 (1245-4530)	3800 (1140-6080)	0.42
Total costs with ART	30592 (28012-53800)	62145 (59401-65337)	<0.01
Total costs without ART	14518 (12422-19910)	15345 (12601-18537)	0.86

Costs: Indian Rupees, Median (Inter Quartile Range); Diagnostic cost: Money spent on laboratory tests and radiology investigation; Drug cost: Money spent for medicines other than Anti-Retroviral Therapy (ART) and ART cost (ART is provided free of cost to all patients. The ART costs are the cost of drugs available commercially); Hospital cost: Include cost spent on registration for hospital visits (In-Patient/Out-Patient/Casualty), consultant visit costs, medical records costs, billing costs and other special costs related to admission; Direct cost: Diagnostic cost+ Drug cost+ Hospital cost; Indirect cost per patient for the whole of one year: food cost+ accommodation cost +travel cost; Total cost: Direct cost + Indirect cost

In the zidovudine group, treatment costs for patients experiencing ADR exceeded the treatment costs for patients who did not experience ADR, although the difference did not achieve statistical significance (14,775 (IQR: 12,568-20,851) vs 12,858 (IQR: 11,909-13,881), p-value: 0.09). In the tenofovir group, treatment costs for patients who experienced ADR was not significantly different compared to patients without ADR (14,076 (IQR: 12,511-15,560) vs 17,171 (IQR: 12,755-19,994), p-value: 0.26). The cost of treating patients with an OI significantly exceeded the corresponding cost among patients without OI in the zidovudine-containing regimen (17,714 (IQR: 13,964-25,719) vs 13,849 (IQR: 11,714-15,883), p-value: 0.01). Among patients receiving the tenofovir-containing regimen, patients with OI spent more money on treatment than among patients without OI, but this difference did not achieve statistical significance (16,472 (IQR: 12,755-30,910) vs 15,183 (IQR: 12,511-17,998), p-value: 0.24).

Strengths and limitations

Strengths: This comparative effectiveness study is a randomized study conducted in a real world scenario from a resource limited setting. This study compares three outcomes (clinical, economic and QoL) between the two available drug regimens for HIV treatment in India. To our knowledge this study is the first study to compare prospectively collected patient level data comparing these two regimens.

Limitations: Though this study was a pragmatic clinical trial, we recruited patients based on inclusion/exclusion criteria. Any patient with any of the excluded health conditions had to be treated with a different ART regimen and could not be included in our study. Although this study was adequately powered for the outcomes of interest, the sample size was comparatively small. This study was conducted at a private tertiary care hospital and patient care in such facilities may differ from other private or government hospitals in India. This study was an unblinded study

and could lead to detection bias. However this study followed the same protocol for detection of side effects and outcome variables for both the treatment groups, thereby reducing bias due to selective detection of outcomes.

2.4 Cost Effectiveness Analysis Comparing Zidovudine and Tenofovir Containing Regimen for HIV in India

Methods

Study population

This study is based on the data collected from a randomized pragmatic unblinded effectiveness clinical trial. The details of the trial are reported in section 2.3. In brief, treatment naïve HIV positive adult patients with asymptomatic HIV infection and no co-morbidities were enrolled, randomized and followed for one year. Clinical outcomes, including development of ADR and OI, viral and immunologic response, adherence to treatment, cost of treatment over one year, and QOL over one year were collected. Outcomes for patients receiving zidovudine - and tenofovir-containing regimens were compared.

Cost calculation

Cost data were collected using established methods for economic analysis in clinical practice [72]. The analysis included both direct and indirect costs. Direct costs reflected medication, diagnosis, and hospital visits, while indirect costs reflected food, accommodation, and travel for both patients and accompanying care givers. Costs were collected for inpatient, outpatient and emergency visits to the study hospital and other health care settings. Costs were recorded in Indian rupees, based on cash receipts and responses gathered from patient interviews. The unit costs for each intervention, diagnostic test, and hospital service are determined annually by the hospital administration and depend on local, geographic and economic factors. The medication costs included the antiretroviral drug costs procured from Emcure Pharmaceuticals Limited for

the purpose of the pragmatic trial and the cost of other drugs prescribed during the course of the treatment. The antiretroviral drug costs were 232 USD for the zidovudine-regimen and 755 USD for tenofovir-containing regimen. Median treatment costs with inter quartile ranges (IQR) were calculated for patients with and without ADR, for patients with and without OI, and for patients with and without both ADR and OI for both regimens.

The payer perspective analysis included the direct costs and the drug costs and excluded indirect costs incurred by the patients. In India the antiretroviral drugs are provided free of cost by the government's free antiretroviral therapy program. Hence the patient perspective sensitivity analysis excluded antiretroviral drug costs.

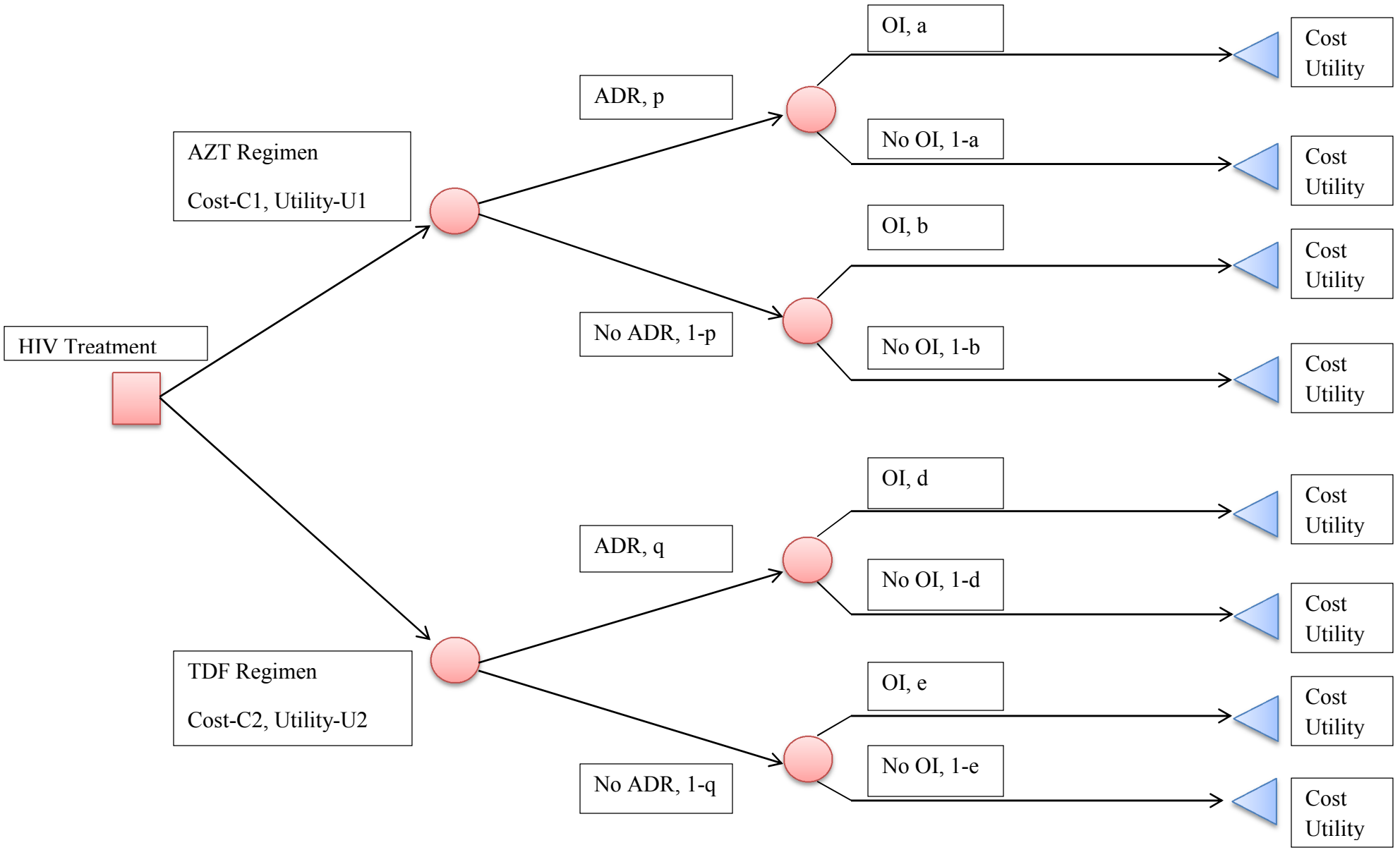
Health Utility Index (QALY)

We used the general European Quality of Life 5 Dimensions (EQ5D) and Medical Outcomes Study (MOS)-36 questionnaires to collect patient centered quality of life information. Responses were collected by a single trained physician from all patients enrolled in the study on a quarterly basis for one year. Both questionnaires have been validated in India and are widely used in patients living with HIV. For the EQ5D, health states were recorded for each dimension, and based on those responses, a utility score was calculated for each respondent using a standardized scoring system [78,79]. Data collected from MOS-36 were converted to the Medical Outcomes Study Short Form 6 Dimensions (SF6D) and utility scores were calculated using a standardized protocol [80,81]. Median utility scores with IQR were calculated for all patients for the one-year follow-up time period, for patients with and without ADR, with and without OI, and with and without both ADR and OI for both the regimens.

Cost effectiveness analysis

The cost effectiveness analysis was performed using a decision tree (Figure 3) and a Markov model (Figure 4) constructed before data collection. The decision tree compared the cost-effectiveness of zidovudine- and tenofovir-containing regimens for treatment of HIV in India. Uncertainty nodes in the tree represent the risk of ADR and the risk of OI, both conditional on the treatment selected. These conditional probabilities were computed using rates computed from the proportions derived from the pragmatic clinical trial using the relationship $p = 1 - e^{-rt}$. Pathway costs and utilities were calculated for all outcome combinations, including toxicity plus OI, toxicity plus no OI, no toxicity plus OI, and no toxicity plus no OI. We rolled back the tree to calculate expected costs and effectiveness as QALYs for each treatment option. The costs, utilities and probabilities included in the decision tree corresponded to a follow-up duration of one year.

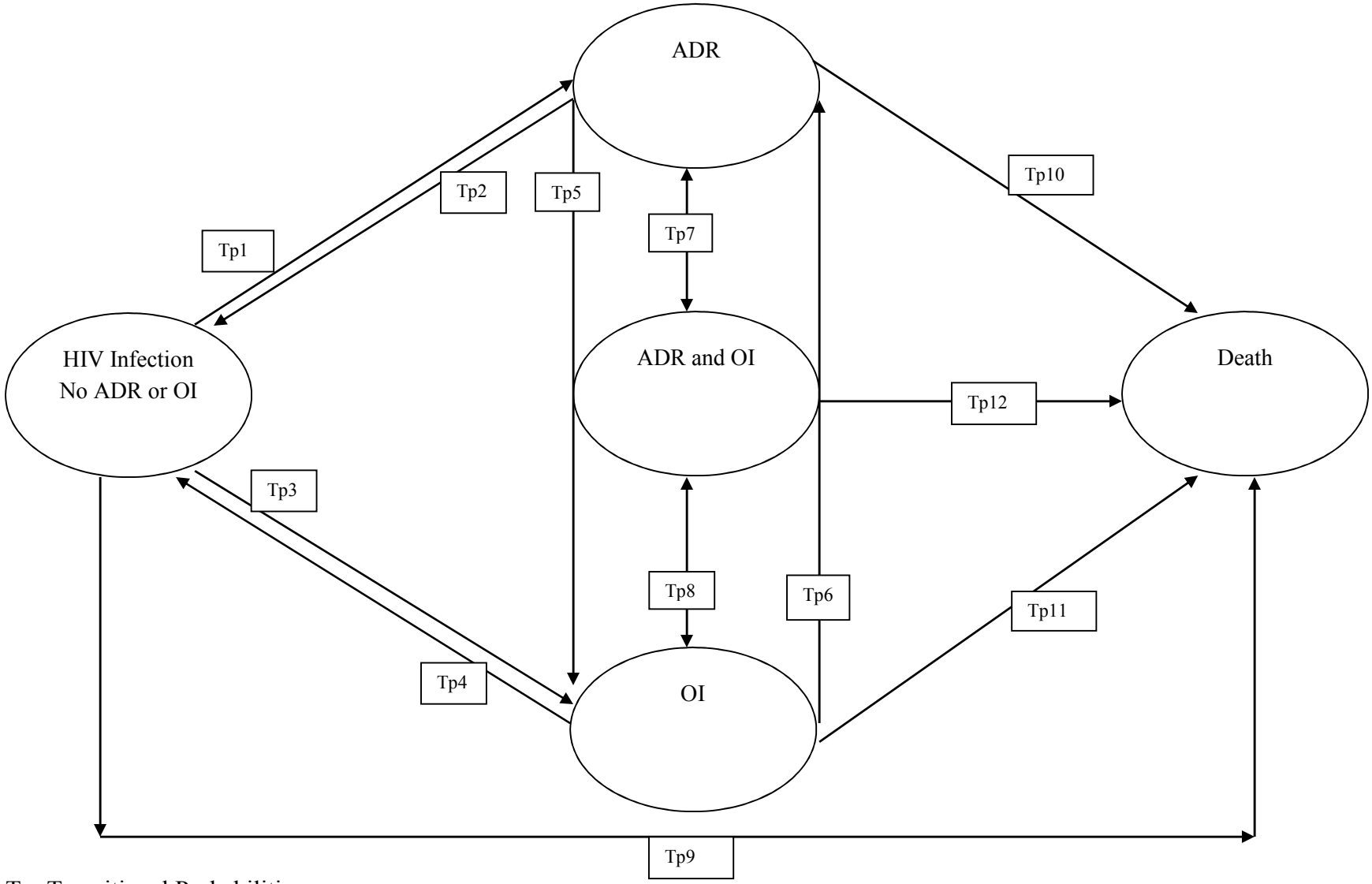
Figure 3: Decision tree for estimating cost effectiveness



ADR- Adverse Drug Reactions, AZT- Zidovudine Containing Regimen, OI- Opportunistic Infections, TDF- Tenofovir Containing Regimen
Incremental cost = C2-C1
Incremental Quality Adjusted Life Year = U2-U1
p: Probability of patients experiencing ADR in AZT containing regimen
1-p: Probability of patients not experiencing ADR in AZT containing regimen
q: Probability of patients experiencing ADR in TDF containing regimen
1-q: Probability of patients not experiencing ADR in TDF containing regimen
a; Conditional probability of patients developing OI with ADR in AZT containing regimen
1-a: Conditional probability of patients not developing OI with ADR in AZT containing regimen
b: Conditional probability of patients developing OI without ADR in AZT containing regimen
1-b: Conditional probability of patients not developing OI without ADR in AZT containing regimen
d: Conditional probability of patients developing OI with ADR in TDF containing regimen
1-d: Conditional probability of patients not developing OI with ADR in TDF containing regimen
e: Conditional probability of patients developing OI without ADR in TDF containing regimen
1-e: Conditional probability of patients not developing OI without ADR in TDF containing regimen

To study the long term changes in costs and effectiveness, we created a Markov model (Figure 4). Human Immunodeficiency Virus infection is a chronic disease condition with repetitive or recurrent adverse drug reactions and opportunistic infections. When treated effectively, HIV does not progress and the level of severity may be contained at much the same level for years. In order to compare the long term costs and health benefits of the two treatments, we developed a Markov model. The prospect of gaining additional clinical data to better inform assumptions beyond year one is very limited. Hence to atleast explore the implications of assuming that the assumptions hold in subsequent years, a Markov model was used. The Markov model included the five states illustrated in Figure 4.

Figure 4: Markov Simulation model for estimating cost effectiveness



Tp: Transitional Probabilities

State A represents patients who are alive and healthy and who have no ADR or OI. These patients move to State B if they develop only ADR, to State C if they develop only OI, to State D if they develop both ADR and OI, and to state E if they die. Annual transitional probabilities were calculated from the pragmatic clinical trial for one year for patients receiving each treatment (zidovudine-containing regimens and tenofovir-containing regimens). A transition matrix was created for each treatment regimen, with each matrix characterizing transitions among the four states: well, ADR only, OI only, and both ADR and OI. We did not include death in the transitional matrix since the pragmatic study was small with a short duration of follow-up and did not capture mortality rates.

Costs and utilities for different states were calculated for each treatment arm using the trial data. Expected costs and utilities for each treatment were calculated by using the simulation to project the proportion of each treatment cohort in each health state. These proportions were used to estimate the expected incurred cost and the expected QALY gain during each year. Summing those annual costs and QALY gains over an 80-year life expectancy yielded lifetime total costs and total QALYs for each treatment arm. Before summing, costs and QALY gains were discounted at an annual rate of 3 percent. In particular, the present value (PV) included in the sum was calculated from the nominal future value (FV) as $PV = \frac{FV}{1.03^t}$, where t is the number of years in the future. A half cycle correction was performed to minimize bias. Finally, incremental costs and QALYs were calculated by subtracting expected costs or QALYs for the zidovudine - containing regimen arm from the corresponding values projected for the tenofovir-containing regimen arm.

An incremental cost effectiveness ratio was calculated as the ratio of the differences in the costs to the differences in QALYs between tenofovir- and zidovudine-containing regimens. The per capita Gross Domestic Product (GDP) for India[82] (1509 USD) was used to identify thresholds of for cost-effectiveness acceptability. As suggested by the World Health Organization's Choosing Interventions that are Cost-Effective (WHO-CHOICE) project [83], an intervention is "cost-effective" if the cost per QALY ratio does not exceed three times the national annual GDP per capita (In the case of India, three times the GDP is 4527 USD); and the intervention is considered to be "highly cost-effective" if its ratio is less than one times the national annual GDP per capita (1509 USD).

Sensitivity analysis

To characterize the impact of uncertainty in the decision model, we performed univariate sensitivity analysis, varying individual input parameters one at a time and recording how these changes influenced the cost-effectiveness estimate calculated from the model's output.

Costs: We designated median cost estimates as the base case values. The cost of the drug regimens used in this analysis was the cost of procuring these drugs from a pharmaceutical company. Sensitivity analyses were conducted using the lower and upper quartile estimates for costs.

QALYs: We designated median SF6D-derived QALY gains as the base case values. Sensitivity analysis was performed using EQ5D-derived utility values. We designated the SF6D-derived QALY values rather than the EQ5D-derived utility values as the base case assumptions because MOS 36 questionnaires are standardized and are more widely used for HIV patients in India.

Probabilities: We designated median probability estimates as base case values. Sensitivity analyses were conducted using the extremes of the 95 percent confidence intervals (truncated at

0.0 and 1.0) for probabilities. The 95 percent confidence intervals were calculated as $p \pm e$, where error $e = 1.96\sqrt{\frac{p(1-p)}{n}}$, p is the mean estimate for the transition probability, and n is the number of observations used to calculate the estimated probability.

Perspective: A sensitivity analysis from the patient perspective was conducted.

Threshold analyses: If the univariate sensitivity analysis for a parameter produced cost-effectiveness ratios in more than one quadrant in the cost-effectiveness analysis plane, the threshold value for the parameter (the value at which the ratio flips between quadrants) was identified.

Results

Study Population

The average age of participants enrolled in the study was 38 years (standard deviation, SD = 7.1) and 44% of the participants were male. Approximately 84% of the participants were married, 68% were employed, and 90% had some kind of formal education. None of the study participant had a high socioeconomic status; instead, subjects had middle (31%) or lower (69%) socioeconomic status. None of the participants had severe disease (stage 4) and 84% of the participants had asymptomatic infection (stage 1) at recruitment. Baseline variables did not differ statistically across the two study arm cohorts (Section 2.3).

Cost (Payer perspective), QALYs and Probabilities

Among patients experiencing ADR, OI, or both OI and ADR, treatment costs were significantly higher for the tenofovir-containing regimen treatment arm than for the zidovudine-containing regimen arm (Table 14).

Table 14: Model Parameters - Costs for payer's perspective and QALY's

Costs in Indian Rupees[a]	**zidovudine containing regimen (AZT)**	**tenofovir containing regimen (TDF)**	**p-value[c]**
Total cost of treatment for one year (n- AZT=35, TDF=33)	28432 (12422-19910)	58881 (56617-60114)	<0.0001
Cost for treating patients with ADR (n- AZT=31, TDF=15)	33630 (25049-53012)	59306 (59061-60018)	<0.0001
Cost for treating patients with OI (n- AZT=16, TDF=10)	39135 (32953-56100)	60228 (58230-72210)	0.003
Cost for treating patients with both ADR and OI (n- AZT=16, TDF=7)	39135 (32953-56100)	60018 (58230-72210)	0.004
Cost for treatment in patients without ADR and OI (n- AZT=19, TDF=26)	25049 (23738-28432)	57956 (55938-59651)	<0.001
QALY[b]			
Sf6D (n- AZT=34, TDF=33)	0.869 (0.843-0.891)	0.857 (0.832-0.898)	0.52
EQ5D (n- AZT=34, TDF=33)	0.949 (0.881-1.0)	0.942 (0.908-0.969)	0.95
SF6D for patients with ADR (n- AZT=30, TDF=15)	0.863 (0.843-0.891)	0.857 (0.832-0.833)	0.36
SF6D for patients with OI (n- AZT=15, TDF=10)	0.871 (0.851-0.897)	0.853 (0.82-0.883)	0.35
SF6D for patients with ADR and OI (n- AZT=15, TDF=7)	0.871 (0.851-0.897)	0.859 (0.814-0.883)	0.31
SF6D for patients without ADR and OI (n- AZT=19, TDF=26)	0.868 (0.843-0.887)	0.857 (0.833-0.908)	0.96

[a] Median costs (Inter-quartile range); [b] Median QALY's (Inter-quartile range); [c]Wilcoxon Rank Sum Test

Among patients receiving the zidovudine-containing regimen, patients experiencing ADR, OI, or both ADR and OI had significantly higher treatment costs than patients who did not. In the tenofovir-containing regimen arm, cost differences between those patients without ADR and both ADR and OI did not statistically differ from the corresponding costs for patients who did experience those outcomes. However, the costs differed significantly between patients with and without OI (Table 15).

Table 15: Comparison of costs and QALY's with and without ADR, OI, and OI and ADR

	Median Costs in Indian Rupees (Inter-quartile range)	p-value	Median QALY measured by SF6D (Inter Quartile Range)	p-value[a]
	zidovudine containing regimen			
With ADR (n=31)	33630 (25049-53012)	0.03	0.863 (0.843-0.891)	0.54
Without ADR (n=4)	24027 (23409-25811)		0.887 (0.815-0.908)	
With OI (n=16)	39135 (32953-56100)	0,002	0.871 (0.851-0.897)	0.64
Without OI (n=19)	25049 (23738-28432)		0.868 (0.843-0.887)	
With OI and ADR (n=16)	39135 (32953-56100)	0.002	0.871 (0.851-0.891)	0.64
Without OI and ADR (n=19)	25049 (23738-28432)		0.868 (0.843-0.887)	
	tenofovir containing regimen			
With ADR (n=15)	59306 (58061-60018)	0.57	0.857 (0.832-0.833)	0.6
Without ADR (n=18)	57821 (56345-60858)		0.856 (0.825-0.908)	
With OI (n=10)	57851 (55903-59413)	0.01	0.853 (0.82-0.883)	0.51
Without OI (n=23)	60228 (58230-72210)		0.857 (0.832-0.908)	
With OI and ADR (n=10)	60018 (58230-72210)	0.05	0.859 (0.814-0.833)	0.37
Without OI and ADR (n=23)	57956 (55938-59651)		0.857 (0.833-0.908)	

[a]Wilcoxon Rank Sum Test; ADR-Adverse Drug Reaction; OI-Opportunistic Infection; SF6D-Short Form 6 Dimensions; QALY- Quality Adjusted Life Years

The QALY estimates based on either the SF6D or EQ5D indices were similar for patients on the two regimens (Table 14). Nor did QALY gains differ when comparing patients with no OI or ADR or both ADR and OI to patients in the same treatment arm with any combination of OI or ADR (Table 15). The transitional probabilities indicate that a greater proportion of patients receiving the zidovudine-containing treatment regimen experienced ADR or OI than among patients receiving the tenofovir-containing regimen (Table 16). The proportion of patients recovering post OI or ADR was greater in the zidovudine-containing regimen treatment arm compared to the tenofovir containing regimen arm.

Table 16: Model Parameters – Number of patients transitioning between states and Transitional probabilities with standard deviation

Number of patients transitioning between states on zidovudine containing regimen					
	Well	ADR	OI	ADR and OI	Dead
Well	-	31	16	0	0
ADR	31	-	2	5	0
OI	13	2	-	4	0
ADR and OI	0	5	4	0	0
Dead	0	0	0	0	0
Number of patients transitioning between states on tenofovir containing regimen					
	Well	ADR	OI	ADR and OI	Dead
Well	-	15	9	0	0
ADR	14	-	0	2	0
OI	9	0	-	2	0
ADR and OI	0	2	2	-	0
Dead	0	0	0	0	0
Transition Matrix for patients on zidovudine containing regimen					
	Well	ADR	OI	ADR and OI	Dead
Well	0.047	0.587±0.163	0.366±0.16	0	0
ADR	0.587±0.163	0.252	0.028±0.054	0.133±0.112	0
OI	0.310±0.153	0.055±0.076	0.527	0.108±0.102	0
ADR and OI	0	0.133±0.112	0.108±0.102	0.759	0
Dead	0	0	0	0	1
Transition Matrix for patients on tenofovir containing regimen					
	Well	ADR	OI	ADR and OI	Dead
Well	0.397	0.365±0.164	0.238±0.145	0	0
ADR	0.345±0.162	0.597	0	0.058±0.08	0
OI	0.245±0.146	0	0.695	0.059±0.08	0
ADR and OI	0	0.058±0.08	0.058±0.08	0.884	0
Dead	0	0	0	0	1

ADR- Adverse Drug Reaction; OI- Opportunistic Infection

Cost Effectiveness Analysis

Payer perspective

The decision tree analysis projected results for a period of one year. Compared to the zidovudine-containing regimen, the tenofovir-containing regimen had an incremental cost of 8,091 Indian Rupees (INR) and a gain of 0.02 SF6D-derived QALYs, yielding a cost-effectiveness ratio of 404,550 INR (6,525 USD) per QALY. Using the EQ5D in place of the SF6D to estimate utility weights reduced the estimated QALY gain The incremental cost and health benefit to a gain of 0.009 QALYs, and hence increased the cost-effectiveness ratio to 899,000 INR (14,500 USD) per QALY.

The Markov model was stopped at the 13th cycle when age exceeded 80 years. The base case Markov model projected an incremental cost of 1,768,000 INR (28,521 USD) and a health benefit of 0.08 QALYs. The corresponding cost-effectiveness ratio was 22,104,000 INR (356,511) per QALY. The results suggest that the tenofovir-containing regimen is not cost effective compared to the zidovudine-containing regimen with respect to the WHO-CHOICE criteria.

Sensitivity Analysis

Sensitivity analysis suggests that the results of this study are relatively robust when assumptions are varied. Fifty-eight univariate sensitivity analyses were performed. All the analyses continued to project that the tenofovir-containing regimen incurs positive incremental costs, and 52 of the analyses (90%) continued to project a QALY gain for patients on tenofovir containing regimen. The following univariate sensitivity analysis produced cost-effectiveness ratios in more than one quadrant: univariate sensitivity analysis for transitional probabilities from well to adverse drug reaction, well to opportunistic infections, adverse drug reactions to well, adverse drug reactions to both ADR and OI, opportunistic infections to well and opportunistic infection to both ADR and OI in both the zidovudine and tenofovir regimen arms. The corresponding threshold values were identified (Table 17). The analysis also showed that the tenofovir-containing regimen was cost effective so long as its cost is less than 440 USD.

Table 17: Cost savings and QALY gained: tenofovir regimen versus zidovudine regimen: base case and sensitivity analysis

Assumption	Range*	Threshold	25% Assumption		75% Assumption	
			Δ Costs	Δ QALY	Δ Costs	Δ QALY
Discount	1% to 5%	NA	1,813,719	0.09	1,858,108	0.05
Costs						
Zidovudine Regimen						
Well		NA	1,791,009	0.08	1,709,693	0.08
With ADR		NA	1,954,791	0.08	1,347,065	0.08
With OI		NA	1,883,275	0.08	1,435,657	0.08
With ADR and OI		NA	1,838,713	0.08	1,575,061	0.08
Tenofovir Regimen						
Well		NA	1,723,405	0.08	1,806,006	0.08
With ADR		NA	1,739,933	0.08	1,784,520	0.08
With OI		NA	1,726,067	0.08	1,984,158	0.08
With ADR and OI		NA	1,755,766	0.08	1,853,752	0.08
Probabilities						
Zidovudine Regimen						
Well to ADR		0.586	1,413,285	-11	2,131,719	10.7
Well to OI		0.365	1,458,245	-10.5	2,108,120	10.5
ADR to Well		0.635	1,750,607	0.41	1,782,297	-0.18
ADR to OI		NA	1,778,626	0.06	1,757,739	0.1
ADR to ADR and OI		0.085	1,812,629	-0.12	1,734,323	0.24
OI to Well		0.354	1,719,558	0.4	1,803,472	-0.18
OI to ADR		NA	1,753,243	0.11	1,780,822	0.06
OI to ADR and OI		0.037	1,782,622	-0.04	1,757,303	0.18
ADR and OI to ADR		NA	1,740,772	0.18	1,783,451	0.01
ADR and OI to OI		NA	1,761,017	0.14	1,767,333	0.03
Tenofovir Regimen						
Well to ADR		0.395	1,764,310	0.62	1,646,053	-4.1
Well to OI		0.262	1,757,021	0.6	1,776,704	-0.36
ADR to Well		0.318	1,772,531	-0.48	1.765,357	0.48
ADR to OI		NA	1,768,298	0.08	1,768,298	0.48
ADR to ADR and OI		0.093	1,756,039	0.3	1,773,087	-0.09
OI to Well		0.1	1,773,488	-0.5	1,745,022	0.167
OI to ADR		NA	1,768,298	0.08	1,768,298	0.08
OI to ADR and OI		0.131	1,766,896	0.2	1,769,391	-0.008
ADR and OI to ADR		NA	1,769,771	0.03	1,767,151	0.12
ADR and OI to OI		NA	1,768,661	0.05	1,768,001	0.1

* 25^{th} and 75^{th} percentile for all assumptions unless otherwise noted

NA-Cost effectiveness ratio remains in the same quadrant for values in tested range for this assumption

ADR-Adverse Drug Reactions; OI-Opportunistic Infections;

Cost gained (Δ Costs) = cost for tenofovir containing regimen minus cost for zidovudine containing regimen in Indian Rupees

Quality Adjusted Life Years (QALY) gained (Δ QALY) = QALY for tenofovir containing regimen minus QALY for zidovudine containing regimen measured by SF6D (Short Form 6 Dimensions Questionnaire)

Model stopping criteria: Life years gained above 80

Patient perspective

Decision tree projections from the patient perspective yielded an average cost savings of 4,596 INR and a gain of 0.02 QALYs for the tenofovir-containing regimen. The Markov model projected a cost savings of 44,413 INR and a net gain of 0.08 QALYs at the end of 13 cycles.

DISCUSSION AND FUTURE DIRECTIONS

This PhD thesis, a comparative effectiveness study comparing the current first line treatment regimen (zidovudine-containing regimen) versus the alternate first line treatment regimen (tenofovir-containing regimen) for treating patients living with HIV in India demonstrates that, patients receiving a tenofovir-containing regimen experience fewer adverse drug reactions compared to patients receiving an zidovudine-containing regimen and the proportion of patients requiring regimen change due to adverse drug reactions was smaller for the tenofovir-containing regimen than for zidovudine-containing regimen. With treatment, opportunistic infections were less frequent in patients receiving the tenofovir-containing regimen than among patients receiving the zidovudine-containing regimen. The CD4 cell count increased with antiretroviral therapy in both regimens, however the incremental value did not differ between the two drug regimens. At the end of one year of treatment patients receiving both the regimens had a similar increase in body mass index, but with long-term antiretroviral therapy, patients on the tenofovir-containing regimen tended to gain more body mass index than those on the zidovudine-containing regimen. The proportion of patients with treatment failure was similar between the two regimens. Adherence to antiretroviral therapy exceeded 90% in both the treatment arms. The quality of life improved steadily in patients receiving both the regimens immediately after treatment initiation, but with long-term treatment the quality of life decreased in patients receiving the zidovudine-containing regimen. The cost of treatment of adverse drug reactions and opportunistic infections was higher in patients receiving the zidovudine-containing regimen than in patients receiving the tenofovir-containing regimen. Patients on the zidovudine-containing regimen had to spend approximately one-third of their income earned on their antiretroviral therapy. The tenofovir-containing regimen was not cost effective compared to the

zidovudine-containing regimen from payer perspective. However, tenofovir-containing regimen saved costs and improved health from patient perspective.

Adverse drug reactions are one of the major concerns with zidovudine-containing regimen. Our studies have shown that patients receiving the zidovudine-containing regimen have significantly higher rates of adverse drug reactions compared to patients receiving tenofovir-containing regimen, which is consistent with the data from India and other countries[25,27,32,35]. Larger proportions of patients on antiretroviral therapy with adverse drug reactions require regimen change to a less toxic regimen. Our observational study showed an overall regimen change of 60% in patients receiving antiretroviral therapy with adverse drug reactions which was consistent with the SWITCH study finding that showed a regimen change of 61% from cohort studies[28]. Similar to other studies[31,32,35] our study also showed that larger proportion of patients receiving the zidovudine-containing regimen required a regimen change due to adverse drug reaction compared to the tenofovir-containing regimen. Zidovudine induced anaemia is the most frequent of the major adverse drug reactions in patients receiving the zidovudine-containing regimen[25-27]. Tenofovir induced renal toxicity is the major adverse drug reactions in patients receiving the tenofovir-containing regimen[28,33,75,84]. Our study documented zidovudine induced anemia in 49% of the patients receiving zidovudine-containing regimen. Likewise, we documented tenofovir induced renal toxicity in 3% of the patients receiving the tenofovir-containing regimen, which is consistent with the results from other studies that have documented renal toxicity in up to 8% of the patients receiving tenofovir-containing regimen[30,75]. Another adverse effect of concern for tenofovir use is a decrease in bone density; however the study duration in this thesis was too short to comment on this adverse event. A Cochrane review [34] including two clinical trials showed that there was no difference in the rate of ADRs between zidovudine- and tenofovir-

containing regimens. However, both the studies included in the review were from resource sufficient settings with a longer duration of follow-up and a larger sample size. The zidovudine- and tenofovir-containing regimens in the two studies also differed in terms of drug composition. This pragmatic study included all patients with toxicity and did not categorize them according to the severity of the toxicity experienced. For the other agents in the regimens (lamivudine and emtricitabine) the adverse drug reactions are considered to be comparable and the adverse effects of nevirapine and efavirenz are distinctive.[85]

In both the observational study and the pragmatic trial patients receiving the tenofovir-containing regimen tend to experience fewer opportunistic infections than patients receiving the zidovudine-containing regimen. These findings suggest that the tenofovir-containing regimen has a better overall treatment effect than the zidovudine-containing regimen. The number of patients requiring in-patient admissions was similar between regimens in both the studies.

The CD4 counts did not differ between patients on either regimen at the initiation of therapy and at the end of follow-up in both the studies. There was no difference in change in the CD4 levels between the two regimens. Studies from resource limited settings have documented greater immunologic parameter improvement among patients receiving tenofovir-containing regimens, than among patients receiving zidovudine-containing regimens[31,34,35]. A systematic review demonstrated reduction in treatment failure with tenofovir-containing regimens[86], while a multicenter randomized trial showed that patients receiving both tenofovir-and zidovudine-containing regimens have similar treatment failure outcomes[33]. In both of our studies the number of patients with treatment failure was similar between regimens.

Adherence to treatment was similar between regimens in both of our studies. Studies have shown that good adherence to treatment has a positive impact on the CD4 levels[43,44] and on the quality

of life[45]. Both the treatment regimens used in this study are single combination pills that are easier to take and patients on single pill combination regimens tend to be more adherent to antiretroviral therapy [46,47].

Our observational study with a follow-up of three years showed that patients on the tenofovir-containing regimen had a higher body mass index at the end of follow-up compared to those on the zidovudine-containing regimen. However, there was no difference in change in body mass index during the one year period of treatment between the two regimens in the pragmatic trial. This lack of difference in change in body mass index in the pragmatic study suggests that the study participants may have been healthier with a more normal nutritional status at baseline. These patients may not have lost a significant amount of weight prior to treatment in both the regimens.

The mean quality of life for a period of one year was similar between the regimens. A randomized control trial from resource sufficient settings also showed no difference in the quality of life between regimens at the end of follow-up[87]. However, there was a steady increase in the quality of life in patients receiving the tenofovir-containing regimen whereas among patients receiving the zidovudine-containing regimen, it increased during the first few months of treatment and then declined towards the end of the one-year treatment period.

The overall treatment costs for a period of one year was similar between regimens. However, the cost of treatment was higher in patients experiencing adverse drug reactions and opportunistic infections in the zidovudine arm. This result is consistent with our assumptions based on the results from the pilot study that showed that patients with adverse drug reactions spend significantly more money than patients without adverse drug reactions. Treatment costs in patients with and without adverse drug reactions and opportunistic infections did not differ in the

tenofovir arm. Cost effectiveness analysis using both short-term (decision tree) and long-term (Markov simulation) CEA modeling techniques showed cost savings and improvement in quality adjusted life years with tenofovir-containing regimen with patient perspective. However, tenofovir regimen was not cost effective from payer perspective.

Studies from both resource-sufficient and resource-limited settings have shown that the tenofovir-containing regimen is cost effective compared to the zidovudine-containing regimen. A similar study using primary data from Spain showed that over one year of follow-up, the zidovudine-containing regimen was more cost effective than the tenofovir-containing regimen from a societal perspective. However, over a more extended follow-up period, the two regimens produced similar economic outcomes [62]. Another CEA conducted from a societal perspective and also from Spain showed that patients receiving the tenofovir-containing regimen use fewer resources and have lower treatment costs than patients receiving a zidovudine containing regimen [63]. However data for this study was taken from a large trial comparing these two regimens and follow-up was under two years. A study from India showed that the tenofovir-containing regimen was cost effective compared to no treatment. This study performed a Monte-Carlo simulation and used data from observational and clinical trials from both India and the United States. The cost of the tenofovir containing regimen for this study was obtained from the Clinton foundation and was approximately 168 USD per patient per year. In our study we used the cost of the tenofovir-containing regimen that was paid to the pharmaceutical company for procurement of the drug (755 USD). Sensitivity analysis showed that the tenofovir-containing regimen was cost effective if its cost was less than 440 USD.

In resource limited settings like India, the ART drugs are provided for free to patients registered under the Government sponsored ART program. In case of complications due to ADR or OI,

patients with sufficient financial resources receive treatment from private hospitals and pay for their own treatment, while other patients receive free treatment from government hospitals. While patients pay direct costs in private hospitals, including costs for medications, laboratory and radiological expenses, the government covers these costs for patients in government hospitals. Including tenofovir-containing regimen as the first line treatment in the government of India sponsored antiretroviral therapy program will improve the efficiency of health care in government-supported hospitals. Drug costs used in this study were from a pharmaceutical company and may not reflect the cost of drugs that are procured by the government antiretroviral therapy program. Future cost effectiveness analysis using drug procurement costs from the free government antiretroviral program will provide more insights on implementing tenofovir-containing regimen as the first line antiretroviral therapy through the free government sponsored antiretroviral therapy program.

This comparative effectiveness study shows that patients receiving tenofovir-containing regimens have fewer ADRs and OIs and have improved body mass index levels compared to patients receiving zidovudine-containing regimens. The CEA shows that tenofovir-containing regimen is not cost effective compared to the zidovudine-containing regimen from payer perspective. However the drug cost included in this CEA does not reflect the cost of drugs procured by the free antiretroviral therapy program. The government procurement cost may be low enough to make tenofovir-containing regimen cost effective from payer perspective. From patient perspective tenofovir-containing regimen saves costs and improves health in patient living with HIV. Patients on the zidovudine-containing regimen spend approximately one-third of their income for the treatment of ADR and OI. Hence steps should be taken to reduce the

procurement costs for the tenofovir-containing regimen and to implement the tenofovir-containing regimen as the first-line treatment regimen for patients living with HIV in India.

Future Directions

We have studied only one drug in each of these regimens. There are other, newer antiretroviral therapy agents including etravirine, darunavir/ritonavir, lopinavir/ritonavir, atazanavir/ritonavir and raltegravir that might be used in tenofovir-containing regimens. Additional studies of clinical, immunologic and QoL outcomes with these regimens may be of great interest to patients living with HIV in India.

We would like to conduct similar cost effectiveness studies in pediatric patients with HIV infection to compare the current first line treatment regimen (zidovudine-containing regimen) and the alternate treatment regimen (abacavir-containing regimen). Abacavir containing regimens are considered expensive and also have life threatening adverse drug reaction, requiring expensive genetic testing prior to administration of these drugs. Inspite of superior treatment effect, abacavir containing regimen is seldom considered in pediatric patients. We would like to compare these two regimens to recommend the best possible treatment for pediatric patients living with HIV in India.

Comparative effectiveness studies, pragmatic clinical trials and cost effectiveness analysis based on primary data are seldom conducted in resource limited setting since they are considered not feasible and expensive. Hence most of the treatment recommendations are based on studies from resource sufficient settings which may not be extrapolated appropriately to resource limited settings. We have demonstrated the feasibility of conducting these studies in resource limited settings with minimal financial resources. In future we propose to conduct similar studies in

infectious disease and in other medical fields requiring informed decision making in India and other resource limited settings.

REFERENCE

1. NACO. Annual Report 2012-2013, . 2013. http://www.naco.gov.in/upload/Publication/Annual%20Report/Annual%20report%202012-13_English.pdf (accessed 11/10/2014.

2. State Fact Sheets, Department of AIDS Control, Ministry of Health and Family Welfare Government of India, 2014, www.naco.gov.in.

3. WHO Global Health Observatory Data Repository, India Statistics Summary 2002-2013. 2013. http://apps.who.int/gho/data/node.country.country-IND?lang=en (accessed 12/2/2014.

4. WHO. Consolidated Guidelines on The Use of Antiretroviral therapy for treating and Preventing HIV Infection, Recommendations for a Public Health Approach. 2013.

5. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* 2003; **362**(9385): 679-86.

6. Collaboration H-C, Cain LE, Logan R, et al. When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study. *Annals of internal medicine* 2011; **154**(8): 509-15.

7. Collaboration H-C, Ray M, Logan R, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *Aids* 2010; **24**(1): 123-37.

8. When To Start C, Sterne JA, May M, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet* 2009; **373**(9672): 1352-63.

9. Writing Committee for the CC. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Archives of internal medicine* 2011; **171**(17): 1560-9.

10. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *The New England journal of medicine* 2011; **365**(6): 493-505.

11. Strategies for Management of Antiretroviral Therapy Study G, Emery S, Neuhaus JA, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. *The Journal of infectious diseases* 2008; **197**(8): 1133-44.

12. Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS medicine* 2012; **9**(7): e1001270.

13. Golub JE, Durovni B, King BS, et al. Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. *Aids* 2008; **22**(18): 2527-33.

14. Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. *Proceedings of the National Academy of Sciences of the United States of America* 2010; **107**(45): 19485-9.

15. Akinbami A, Dosunmu A, Adediran A, et al. CD4 Count Pattern and Demographic Distribution of Treatment-Naive HIV Patients in Lagos, Nigeria. *AIDS research and treatment* 2012; **2012**: 352753.

16. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to

500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *The New England journal of medicine* 1996; **335**(15): 1081-90.

17. Katzenstein DA, Hammer SM, Hughes MD, et al. The relation of virologic and immunologic markers to clinical outcomes after nucleoside therapy in HIV-infected adults with 200 to 500 CD4 cells per cubic millimeter. AIDS Clinical Trials Group Study 175 Virology Study Team. *The New England journal of medicine* 1996; **335**(15): 1091-8.

18. Saravolatz LD, Winslow DL, Collins G, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the acquired immunodeficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. Investigators for the Terry Beirn Community Programs for Clinical Research on AIDS. *The New England journal of medicine* 1996; **335**(15): 1099-106.

19. Staszewski S, Loveday C, Picazo JJ, et al. Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients. A randomized controlled comparison with zidovudine monotherapy. Lamivudine European HIV Working Group. *Jama* 1996; **276**(2): 111-7.

20. Staszewski S, Miller V, Rehmet S, et al. Virological and immunological analysis of a triple combination pilot study with loviride, lamivudine and zidovudine in HIV-1-infected patients. *Aids* 1996; **10**(5): F1-7.

21. WHO. Antiretroviral Therapy for HIV Infection in Adults and adolescents: recommendations for a public health approach. *WHO library* 2010; **2010 revision**.

22. Journy of ART Programme in India, Story of a Decade, Department of AIDS Control, Ministry of Health and Family Welfare, Government of India, 2014.

http://www.naco.gov.in/upload/Final%20Publications/2014/Journey%20of%20ART%20Programme%20in%20India%20-%20Final.pdf (accessed 12/2/2014.

23. NACO. Antiretroviral Therapy Guidelines for HIV-infected Adults and Adolescents Including Post-exposure Prophylaxis. 2012. http://www.nacoonline.org/About_NACO/Policy_Guidelines.

24. WHO. Consolidated ARV Guidelines. 2013. http://www.who.int/hiv/pub/guidelines/arv2013/art/artmonitoring/en/index3.html.

25. Sivadasan A, Abraham OC, Rupali P, et al. High rates of regimen change due to drug toxicity among a cohort of South Indian adults with HIV infection initiated on generic, first-line antiretroviral treatment. *J Assoc Physicians India* 2009; **57**: 384-8.

26. Sharma A, Vora R, Modi M, Marfatia Y. Adverse effects of antiretroviral treatment. *Indian J Dermatol Venereol Leprol* 2008; **74**(3): 234-7.

27. Agarwal D, Chakravarty J, Chaube L, Rai M, Agrawal NR, Sundar S. High incidence of zidovudine induced anaemia in HIV infected patients in eastern India. *Indian J Med Res* 2010; **132**: 386-9.

28. Davidson I, Beardsell H, Smith B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. *Antiviral Res* 2010; **86**(2): 227-9.

29. Squires K, Pozniak AL, Pierone G, Jr., et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Annals of internal medicine* 2003; **139**(5 Pt 1): 313-20.

30. Jones R, Stebbing J, Nelson M, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. *J Acquir Immune Defic Syndr* 2004; **37**(4): 1489-95.

31. Velen K, Lewis JJ, Charalambous S, Grant AD, Churchyard GJ, Hoffmann CJ. Comparison of tenofovir, zidovudine, or stavudine as part of first-line antiretroviral therapy in a resource-limited-setting: a cohort study. *PLoS One* 2013; **8**(5): e64459.

32. Bygrave H, Ford N, van Cutsem G, et al. Implementing a tenofovir-based first-line regimen in rural Lesotho: clinical outcomes and toxicities after two years. *J Acquir Immune Defic Syndr* 2011; **56**(3): e75-8.

33. Campbell TB, Smeaton LM, Kumarasamy N, et al. Efficacy and safety of three antiretroviral regimens for initial treatment of HIV-1: a randomized clinical trial in diverse multinational settings. *PLoS medicine* 2012; **9**(8): e1001290.

34. Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev* 2010; (10): CD008740.

35. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006; **354**(3): 251-60.

36. Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIV-infected Adult and Adolescent, National AIDS Control Orgization, Ministry of Health and Family Welfare, Government of India. 2007. http://naco.gov.in/upload/Policies%20&%20Guidelines/7-

Guidelines%20for%20Prevention%20and%20Management%20of%20common%20opportunistic%20infections.pdf.

37. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2013.

38. Bentwich Z. Concurrent infections that rise the HIV viral load. *Journal of HIV therapy* 2003; **8**(3): 72-5.

39. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994-2005. *Aids* 2008; **22**(11): 1345-54.

40. Osterberg L, Blaschke T. Adherence to medication. *The New England journal of medicine* 2005; **353**(5): 487-97.

41. Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J, Group VANS. Medication compliance feedback and monitoring in a clinical trial: predictors and outcomes. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2003; **6**(5): 566-73.

42. Spiller B. Methods of assessing and improving compliance in clinical trials. In: Cramer JA SB, ed. Patient compliance in medical practice and clinical trials: New York: Raven Press; 1991: 37-56.

43. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected

persons in clinical trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2002; **34**(8): 1115-21.

44. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *Aids* 1999; **13**(9): 1099-107.

45. Mannheimer SB, Matts J, Telzak E, et al. Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS care* 2005; **17**(1): 10-22.

46. Nachega JB, Parienti JJ, Uthman OA, et al. Lower Pill Burden and Once-Daily Antiretroviral Treatment Regimens for HIV Infection: A Meta-Analysis of Randomized Controlled Trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014; **58**(9): 1297-307.

47. Sax PE, Meyers JL, Mugavero M, Davis KL. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS One* 2012; **7**(2): e31591.

48. Drummond MF, Sculpher. M.J., Torrance, G.W., O'Brien, J.B., Stoddart, L.G. Cost-effectiveness analysis. Methods of Economic Evaluation of Health Care Programmes: Oxford University Press Inc., New York; 2005: 124-6.

49. Neumann PJ, Goldie SJ, Weinstein MC. Preference-based measures in economic evaluation in health care. *Annual review of public health* 2000; **21**: 587-611.

50. Drummond MF, Sculpher. M.J., Torrance, G.W., O'Brien, J.B., Stoddart, L.G. Cost-utility analysis. Methods of Economic Evaluation of Health Care Programmes; 2005: 137-210.

51. Rosenbaum PR, Rubin, D.B. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983a; **70**: 41-55.

52. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research* 2011; **46**(3): 399-424.

53. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. *Stat Med* 2006; **25**(12): 2084-106.

54. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**(19): 2265-81.

55. Rheta E.Lanehart PRdG, Eun Sook Kim, Aarti P. Bellara, Jeffrey D. Kromrey, and Reginald S. Lee. Propensity Score Analysis and Assessment of Propensity Score Approaches Using SAS Procedure. SAS Global Forum 2012; 2012.

56. Austin PC. Type I error rates, coverage of confidence intervals, and variance estimation in propensity-score matched analyses. *The international journal of biostatistics* 2009; **5**(1): Article 13.

57. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Stat Med* 2004; **23**(19): 2937-60.

58. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *The New England journal of medicine* 1977; **296**(13): 716-21.

59. Drummond MF. Experimental versus observational data in the economic evaluation of pharmaceuticals. *Medical decision making : an international journal of the Society for Medical Decision Making* 1998; **18**(2 Suppl): S12-8.

60. Drummond MF, Davies L. Economic analysis alongside clinical trials. Revisiting the methodological issues. *International journal of technology assessment in health care* 1991; **7**(4): 561-73.

61. Ramsey S, Willke R, Briggs A, et al. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2005; **8**(5): 521-33.

62. Sanchez-de la Rosa R, Herrera L, Moreno S. Cost-effectiveness analysis of emtricitabine/tenofovir versus lamivudine/zidovudine, in combination with efavirenz, in antiretroviral-naive, HIV-1-infected patients. *Clinical therapeutics* 2008; **30**(2): 372-81.

63. Fernandez Lison LC, Pujol de la Llave E, Hevia Alonso A, Garrido Martinez MT, Bocanegra Martin C. [Cost-effectiveness analysis of tenofovir versus zidovudine in combination therapy with efavirenz and lamivudine for the treatment of HIV in naive patients]. *Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria* 2005; **29**(1): 11-7.

64. Brogan AJ, Talbird SE, Cohen C. Cost-effectiveness of nucleoside reverse transcriptase inhibitor pairs in efavirenz-based regimens for treatment-naive adults with HIV infection in the United States. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2011; **14**(5): 657-64.

65. von Wyl V, Cambiano V, Jordan MR, et al. Cost-effectiveness of tenofovir instead of zidovudine for use in first-line antiretroviral therapy in settings without virological monitoring. *PLoS One* 2012; **7**(8): e42834.

66. Bender MA, Kumarasamy N, Mayer KH, et al. Cost-effectiveness of tenofovir as first-line antiretroviral therapy in India. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; **50**(3): 416-25.

67. Pappaioanou M, Malison M, Wilkins K, et al. Strengthening capacity in developing countries for evidence-based public health: the data for decision-making project. *Social science & medicine* 2003; **57**(10): 1925-37.

68. Kent DM, McGrath D, Ioannidis JP, Bennish ML. Suitable monitoring approaches to antiretroviral therapy in resource-poor settings: setting the research agenda. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2003; **37**(Suppl 1): S13-24.

69. McMichael C, Waters E, Volmink J. Evidence-based public health: what does it offer developing countries? *Journal of public health* 2005; **27**(2): 215-21.

70. Swingler GH, Volmink J, Ioannidis JP. Number of published systematic reviews and global burden of disease: database analysis. *Bmj* 2003; **327**(7423): 1083-4.

71. Thuppal SV, Karthik R, Abraham OC, et al. Cost Estimation of First-Line Antiretroviral Therapy with Zidovudine/Stavudine as the Nucleoside Backbone in India: A Pilot Study. *J Int Assoc Provid AIDS Care* 2013; **PMCID:24027170**.

72. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. *Jama* 1989; **262**(20): 2879-86.

73. N. Kumar CS, P. Kumar and A.S. Kundu. Kuppuswamy's Socioeconomic Status Scale-Updating for 2007. *The Indian Journal of Pediatrics* 2007; **74**(12): 1131-3.

74. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *Bmj* 2008; **337**: a2390.

75. Szczech LA. Renal dysfunction and tenofovir toxicity in HIV-infected patients. *Topics in HIV medicine : a publication of the International AIDS Society, USA* 2008; **16**(4): 122-6.

76. Kumar N, Shekhar C, Kumar P, Kundu AS. Kuppuswamy's socioeconomic status scale-updating for 2007. *Indian journal of pediatrics* 2007; **74**(12): 1131-2.

77. WHO. Consolidated ARV Guidelines. 2013. http://www.who.int/hiv/pub/guidelines/arv2013/art/artmonitoring/en/index3.html (accessed 1/10/2014.

78. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011; **20**(10): 1727-36.

79. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health policy* 1990; **16**(3): 199-208.

80. McCabe C, Brazier J, Gilks P, et al. Using rank data to estimate health state utility models. *Journal of health economics* 2006; **25**(3): 418-31.

81. Kharroubi S, Brazier JE, O'Hagan A. Modelling covariates for the SF-6D standard gamble health state preference data using a nonparametric Bayesian method. *Social science & medicine* 2007; **64**(6): 1242-52.

82. Fund IM. World Economic Outlook Database, October 2014: Report for Selected Countries and Subjects. 2014. http://www.imf.org/external/pubs/ft/weo/2014/02/weodata/weorept.aspx?sy=2012&ey=2014&scsm=1&ssd=1&sort=country&ds=.&br=1&c=534&s=NGDPDPC&grp=0&a=&pr.x=54&pr.y=12 (accessed 3/3/2015.

83. Organization WH. Cost effectiveness and strategic planning (WHO-CHOICE). 2014. http://www.who.int/choice/en/ (accessed 3/3/2015.

84. Mugomeri E, Olivier D, van den Heever-Kriek E. The effect of tenofovir in renal function in HIV-positive adult patients in the Roma health service area, Lesotho, southern Africa. *Journal of the International AIDS Society* 2014; **17**(4 Suppl 3): 19681.

85. WHO. Pharmacological Equivalance and Clinical Interchangability of Lamivudine and Emtricitabine: A Review of Current Literature. *Technical Update on Treatment Optimization*, 2012. apps.who.int/iris/bitstream/10665/70936/1/9789241503815_eng.pdf (accessed.

86. Tang MW, Kanki PJ, Shafer RW. A review of the virological efficacy of the 4 World Health Organization-recommended tenofovir-containing regimens for initial HIV therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2012; **54**(6): 862-75.

87. Cooper V, Moyle GJ, Fisher M, et al. Beliefs about antiretroviral therapy, treatment adherence and quality of life in a 48-week randomised study of continuation of zidovudine/lamivudine or switch to tenofovir DF/emtricitabine, each with efavirenz. *AIDS care* 2011; **23**(6): 705-13.