# TWO DISEASES (TB/HIV) AND TWO MEDICINES (ATT/ART): ONE PATIENT AND ONE SERVICE!

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## SOURCE

*Salim S. AbdoolKarim et al*, 'Integration of Antiretroviral Therapy with Tuberculosis Treatment', *The New England Journal of Medicine*, N Engl J Med 2011;365:1492-501. Also available at www.nejm.org October 20, 2011, viewed and accessed on 8th Sept 2013 at http://www.nejm.org/doi/pdf/10.1056/NEJMoa1014181

## INTRODUCTION

This review will evaluate the article titled 'Integration of Antiretroviral Therapy with Tuberculosis Treatment' by *Salim S. Abdool Karim* et al published in 'The New England Journal of Medicine'. In the process of summarization -- its purpose will be defined, the structure of the article be examined in terms of ease with which any reader can have access to this piece of information. The article will be anatomized based upon its authority, accuracy, currency, relevance, objectivity and stability in that order. The review will also judge the article's accessibility and credibility. Upon overall assessment the article has been found to be well written, clear and relevant.

## LITERATURE REVIEW

Most probably the first study to assess time until ART initiation in patients before vs. after TB/HIV service integration is done by Bernhard Kerschberger, et al (Kerschberger B, Hilderbrand K, Boulle AM, Coetzee D, Goemaere E, et al. (2012) The Effect of Complete Integration of HIV and TB Services on Time to Initiation of Antiretroviral Therapy: A Before-After Study. PLoS ONE 7(10): e46988. doi:10.1371/journal.pone.0046988)

The highlight of the study by Kerschberger, that TB/HIV integration is feasible in the setting discussed here and shows that positive outcomes for co-infected patients can be realized immediately: Bernhard Kerschberger, et al found that patients who received care through this

integrated model were 60% more likely to initiate ART. These findings have been found to be robust enough to multiple sensitivity analyses.

One more study in the same setting demonstrated that assessment at an ART clinic during TB treatment reduces loss to follow-up by 80%. Hermans et al. reported a decrease of TB treatment default after integration of HIV and TB services in a large urban HIV clinic in Uganda. The approach "*The two diseases, one patient, one service, one appointment, one health care worker*" also enhances clinic staff's expertise and experience in managing co-infected patients and thus can address better –the patients' considerable clinical challenges—that of drug interactions and toxicity, IRIS, TB deterioration and optimal timing of ART initiation. The advantages of initiation will include, adherence and social support interventions within integrated programs which can mutually reinforce each other. Further integration can avoid the duplication of logistic and administrative services thereby improving the efficiency of service delivery.

Recent data from SAPIT trial (the Starting Antiretroviral Therapy at Three Points in Tuberculosis) has shown that initiation of ART during TB treatment enhances the survival for PLHAs (people living with HIV/AIDS) who have $CD4^+$ T cell counts <500 cells/$mm^3$, compared with starting ART after TB treatment is completed.

An innovative strategy has been developed where TB/HIV Co-infected persons receive comprehensive HIV and AIDS services and TB care at the TB clinic for the duration of their TB treatment, with sending them to an HIV program after completion of their TB treatment

A systematic review by LSHTM (The London School of Hygiene & Tropical Medicine) originally a background paper for the WHO- organizing First Global Symposium on Health Systems Research, has been conducted as to how TB and HIV services could be integrated in practice. They have suggested various models of integration of HIV and TB services, the model where the TB and HIV services both are provided as a single, integrated service within a health facility provides benefits to PLHAs in most settings, relative to referral to the other service even for screening. Single, integrated service models can decrease the transportation costs and patient time required to have the both services, and can save the staff time.

In Malawi, Africa, the Martin Preuss Centre have been following the fully-integrated TB-HIV model upon which Lighthouse and LSHTM have jointly conducted a case study of the integration of TB and HIV services. It has proved to be very beneficial for the TB/HIV co-infected patients. At this centre96% of TB patients who has shown HIV positive status in 2009. And has demonstrated good TB treatment outcomes among both -- HIV-positive and HIV-negative patients, to the tune of more than 85% cured or completed treatment. The results at Martin Preuss Centre has proved that high-quality, integrated HIV and TB services can be provided in resource-constrained settings too. So in Malawi the National ART and National TB Programs have integrated their services in all TB/ART management sites across the country.

IHAA (International HIV/AIDS Alliance) too had conducted a survey of Alliance linking organizations to get a view and record the degree and models of integration of HIV and TB services within community organizations. Various models of integration of TB into HIV programs have been defined, and a range of levels of integration were found. After the survey, the IHAA drafted a TB strategy which aims to enhance the integration of TB/HIV activities.

In India a cross-sectional study to evolve the criteria for HIV testing policy for TB patients has also been conducted by NARI (National AIDS Research Institute) It has been come to the notice that many care providers in India are still not advising TB patients to test for HIV, thereby letting go many opportunities for patients to make use of the HIV services they require. NARI, together with LSHTM, has worked on a qualitative study to look for the challenges and opportunities for integrating TB and HIV services for TB/HIV co-infected patients.

In South Africa LSHTM and the Aurum Institute have collaborated to conduct 'Evidence for Action-related retrospective and prospective studies' to assess the practices in screening for active TB in HIV+persons

The retrospective studies have found that TB symptoms were common among the HIV-infected adults taking ART but very few symptomatic people were appropriately referred vice versa for TB investigation. The prospective studies have shown that a very high percentage of undiagnosed TB existed among PLHAs presenting for ART. Isoniazid Preventive Therapy (IPT) has been demonstrated to be effective in preventing TB among people living with HIV. LSHTM and the Aurum Institute (in South Africa) are working now on, an Evidence for Action-related qualitative study into the barriers and constraints in the implementation of IPT (Isoniazid Preventive Therapy), where TB/HIV co-infection is rampant. The IPT study has identified major provider -related barriers in implementing Isoniazid Preventive Therapy in form of lack of knowledge and experience, benefits of IPT not known, and uncertainty about the availability of guidelines.

In Asia and sub-Saharan Africa many RCTs are being conducted to know the optimal time to initiate ART in PLHAs (people living with HIV/AIDS) who are newly diagnosed with active TB and are eligible to startantiretroviral therapy. These studies are to compare patients starting antiretroviral therapy within thefirst 4 weeks versus 8–12 weeks of initiation of TB treatment. A trial in South Africa has confirmed the current WHO recommendations which advise the patients to start ART and not to wait until completion of TB treatment. Mortality rates have been found to be significantly higher among PLHAs who initiated antiretroviral therapy after completion of TB treatment, compared to those who start within the first two months of intensive phase TB treatment (under RNTCP –Revised National TB Control Program in India) or after completing intensive phase TB therapy In Cambodia among 661 patients were found to have a reduction of mortality of 34%if antiretroviral therapy was initiated in the first two weeks of TB treatment compared to eight weeks A cohort of 313 Spanish patients have demonstrated that initiating ART

in the first two months of TB treatment, was an independent predictor of survival compared to starting antiretroviral treatment after three months of TB treatment

## ARTICLE SUMMARY

The objective of this article is to consider if the integration of Anti Retroviral Thearpy (ART) with Tuberculosis Treatment could reduce the mortality and to determine the optimal timing of initiation of ART during tuberculosis treatment. To implement earlier ART initiation could be done through integration of TB and HIV services, which could be a more efficient model of care than a separate, vertical program. TB is the the commonest Opportunistic Infection (OIs) and a leading cause of morbidity and mortality among PLHAs in almost all parts of the world. The importance and requirement for collaboration between TB and HIV services is being recognized internationally as patients with TB/HIV co-infected often have to navigate two separate health care programs, which can considerably increase the time and transportation costs associated with acquiring the health care. It is utmost that both TB and HIV services are effectively coordinated to ensure the TB/HIV co-infected persons have the access to the care they require from both services to ensure the best results

According to this article, the early initiation of ART in patients with CD4+ T-cell counts of < $50/mm^3$ increased AIDS-free survival. Deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS(Immune Reconstitution Inflammatory Syndrome) and other adverse events related to ART without increasing the risk of AIDS or death The current WHO recommendations to initiate ART as soon as possible after the start of tuberculosis treatment, regardless of the CD4+ T-cell count, may need to be revisited in view of the findings of this study.

## ARTICLE STRUCTURE

The article starts with an abstract that presents an effective overview of the article by establishing the background to the issue of TB/HIV integration and related points. The article itself is very qualitative in nature and is ten pages long. It is accessible online as a PDF documented the contact details for the authors are adequately provided. There is a logical ordering of points and both the paragraphs and the sentences are just informative making the availability of the information, its reading and understanding all the easier. The conclusion is a straightforward summary of the points made. There are adequate references are provided in a reference section. (16-sixteen references in total). Overall the abstract is effective and, the structure of the article makes it simple and smooth to interpret and understand.

# ARTICLE CRITIQUE

## *AUTHORITY*

The article has been featured in an extremely reputable *source 'The New England Journal of Medicine'* (*NEJM*) which is an English-language peer-reviewed medical journal published by the Massachusetts Medical Society and it is among one of the most prestigious and the oldest published medical journal in the world, which publishes editorials, papers on original research, review articles, correspondence, and case reports, This journal aims to inform and educate, the medical community –its main audience. In addition the fact that the article was found in Cochrane Library with Access Number PUBMED 22010915, which is known to be a reliable database, adds to its credibility. Furthermore it is to be noted that the Cochrane Collaboration organizes medical research information in a systematic way in the interests of evidence-based medicine and conducts systematic reviews of randomized controlled trials of health-care interventions, which it publishes in the Cochrane Library. The main author Dr. Salim S. AbdoolKarim, MD, PhD, is a a world known personality in the HIV fraternity and a clinical infectious diseases epidemiologist whose research interests have been in microbicides and vaccines to prevent HIV infection, and implementation of ART in resource poor settings. In addition to his faculty position as professor of Clinical Epidemiology at the Mailman School, he is pro vice-chancellor (Research), University of KwaZulu-Natal and Director of CAPRISA - Centre for the AIDS Program of Research in South Africa. Dr. Abdool Karim pioneered the NIH-funded HPTN 035 microbicide trial which revealed the potential of anionic polymer, PRO2000, in preventing HIV infection in women. His research on TB-HIV treatment has influenced and continues to shape the clinical management of co-infected patients. He has published widely on infectious diseases, including HIV/AIDS, and co-edited the textbook that is used extensively to teach epidemiology in South Africa. Dr. Abdool Karim is chairperson of the WHO Scientific Advisory Group for Reproductive Health and is a member of the WHO Expert Advisory Panel on Sexually Transmitted Infections and HIV. The contact details of the author are adequately displayed on the article. The reviewer (myself) has heard him and his wife, the co-author of this article, Dr. Quarraisha Abdool Karim, and had the opportunity to meet them at a HIV Conference in Mumbai All of this information indicates that the article is highly plausible

## *ACCURACY*

Being published as an 'original article' in a renowned medical journal of the stature of 'the New England Journal of Medicine' proves its precision. The article has 16 references of articles written by some of world famous HIV Experts like Dr. Cohen and Dr. Meyer implies greatly enhances accuracy and credibility.

## *CURRENCY*

The Journal (NJEM) with this article was published in October 2011, its references date from 1998 to 2010. These dates indicate that the article is very current, as does the content of the article which deals with the latest developments in TB –HIV co-infection treatment.

## *RELEVANCE*

It has been written to provide information for an educated sector (medical doctors) and published in a reputable journal (NEJM) and it is relevant to its main intended audience –the HIV health care providers. The topic covered is also a significant one in the context of HIV Care Support and Treatment (CST). TB is the most common Opportunistic Infection (OIs) in a HIV patient In patients with TB/HIV Co-infection, antiretroviral therapy (ART) may be initiated at the same time as or soon after the initiation of anti- tubercular treatment(ATT). Generally antiretrovirals (ARVs) are often deferred until after the intensive phase of tuberculosis treatment (RNTCP – Revised National TB Control Program in India) because of concerns about the Immune Reconstitution Inflammatory Syndrome (IRIS), a high pill burden, and overlapping side effects when 3 antiretroviral agents are added to the standard 4 anti tubercular drugs (totaling 7 drugs). These challenges may result in interruption or discontinuation of treatment for the acquired immunodeficiency syndrome (AIDS) or tuberculosis (TB), which can lead to drug resistance and potentially limit future therapeutic options. The disadvantages must be weighed against the risk of increased mortality early in the treatment of tuberculosis. The conclusions of the article shows that early initiation of ART in patients with CD4+ T-cell counts of less than 50 cells/$mm^3$ increased AIDS-free survival. Deferral of the initiation of ART to the first 4 weeks of the continuation phase of tuberculosis therapy in those with higher CD4+ T-cell counts reduced the risks of IRIS and other adverse events related to ART without increasing the risk of AIDS or death. The article touches almost all aspects of TB/HIV and it relates to the global community as HIV and TB both are global issues.

## *OBJECTIVITY*

The information in the article was derived from team of authors' extensive experience working at higher centers of excellence in HIV arena -- Centre for the AIDS Program of Research in South Africa (CAPRISA) South Africa, associated with the Department of Epidemiology and the International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University, New York; and Yale University, New Haven USA, The article shows research decisions, and contains both facts and evidences. Opinions have been presented on both sides of the argument (early and late initiation of ART (Anti Retroviral Therapy) at different CD 4+ T cell counts; levels less & more than 50/$mm^3$) are exemplified. The article acknowledges the limitations of the study adequately (3-4 in number). The majority of the claims and arguments made have been supported in the articles and references. The article serves its purpose as an objective presentation of the early vs late initiation of ART in TB-HIV Co-infected patient at

different CD4+ T levels to the medical community in general and HIV Care providers in particular.

## *STABILITY*

Published in a reputed medical journal and available in both print and electronic forms, it can be found on an established and highly credible academic database: The Cochrane Library. For these reasons, the article is stable as a resource and being accessible through a credible and reliable academic database.

## *ANALYSIS OF GRAPH*

Not applicable

## *RECENT ADVANCES RELATED TO THE TOPIC*

There are few studies clarifying the timing of ART initiation in relation to TB treatment start such as -- SAPIT (Starting ART at 3 Points in TB), CAMELIA(Cambodian Early versus Late Introduction of Antiretroviral Drugs), and ACTG 5221 STRIDE studies (Stimulant Reduction Intervention using Dosed Exercise)

All these studies show reduction of mortality and AIDS progression. As we find in patients with CD4 counts of <50 cells/μL, initiation of ART within 2-4 weeks of TB treatment start was associated with a reduction of the combined endpoint of mortality and AIDS progression by 68% in SAPIT and 42% in STRIDE. The CAMELIA study, which enrolled patients with CD4 counts of <200 cells/μL, found a reduction in mortality of 34% with initiation of ART within 2 weeks of TB treatment start in all enrolled patients, regardless of CD4 cell count; however, the median CD4 count was quite low at 25 cells/μL). Collectively, these data indicate that ART should be started very shortly after TB treatment initiation in TB patients with advanced HIV disease. In those with higher CD4 cell counts, it may be safe to defer ART for 2-8 weeks after ATT (Anti Tubercular Therapy) start, but ART should not be delayed until after completion of TB treatment. Importantly, early initiation did not impair HIV RNA suppression in these studies.

The need for early initiation of ART will require coordination between TB care and HIV care, along with increased vigilance for drug toxicities, education about adherence to multiple drugs, and anticipation of increased rates of immune reconstitution syndrome (IRIS)

On the other hand timing of ART in patients with CNS TB disease remains grey. A Vietnamese study of HIV-infected patients with TB meningitis did not find a mortality benefit at 9 months with early (at time of study entry) vs after (2 months after study entry) ART initiation. Mortality in both groups was too high: 55% and 60%, respectively, 9 months after randomization, with the majority of deaths occurring within the first month. As TB meningitis itself can be particularly challenging to diagnose, HIV care providers must retain a high index of suspicion for it and

monitor patients with CNS disease closely, given the poor outcomes associated with this disease. The potential for problems to occur when anti-TB medications and ARV agents are administered concurrently exists. In addition to the drug-drug interactions, the medications may have overlapping toxicities and ascertaining which medication is the offending agent can itself be very be challenging.

As per one article published in BMC Infectious Disesase. 2012 Jul 31;12:168. titled '*Early versus delayed initiation of antiretroviral therapy for Indian HIV-Infected individuals with tuberculosis on anti tuberculosis treatment*.' by Sinha S*, et al.* of Department of Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi has arrived at conclusion 'Early initiation of HAART' for patients with HIV and TB significantly decreases incidence of HIV disease progression and has good tolerability.

This year (June 2013) WHO has issued the most latest recommendations on the initiation of ART in a TB –HIV co-infected persons. As per WHO, among PLHAs, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should be provided to all people with HIV with active TB disease. HIV care settings should implement the WHO Three I's strategy: *Intensified TB case-finding, Isoniazid preventive therapy (IPT) and Infection control at all clinical encounters.*

With only 40% of the people with active TB being tested for HIV, Multidrug-resistant TB (MDR-TB) is an added menace for patients with HIV. MDR-TB/HIV patients face most complicated clinical management, fewer treatment options and poorer treatment outcomes. With limited information being available about the association between HIV and MDR-TB at the population level, MDR-TB/HIV have been found in hospital and other settings, especially in Eastern Europe and in Southern African countries with a high HIV prevalence.

The burden of MDR-TB should be reduced by strengthening HIV prevention, improving infection control and improving collaboration between HIV and TB control activities, with special attention to the groups at the highest risk of MDR-TB and HIV infection, such as people who inject drugs and those exposed in congregate settings.

*Key selected existing recommendations of WHO: Timing of ART for adults and children with TB (from* http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html*)*

- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of the CD4 count (strong recommendation, low-quality evidence)
- Anti- tuberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, moderate quality evidence).

- The HIV-positive TB patients with profound immune-suppression (such as CD4 counts less than 50 cells/$mm^3$) should receive ART immediately within the first two weeks of initiating TB treatment. ART should be started in any child with active TB disease as soon as possible and within eight weeks following the initiation of anti- tuberculosis treatment irrespective of the CD4 count and clinical stage (strong recommendation, low-quality evidence).

- Efavirenz should be used as the preferred NNRTI in patients starting ART while on anti - tuberculosis treatment (strong recommendation, high-quality evidence).

- WHO recommends ART for all patients with HIV and drug-resistant TB, requiring second-line anti-tuberculosis drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of anti-tuberculosis treatment (strong recommendation, very-low-quality evidence).

## CONCLUSION

The review epitomizes and critically reviews S.S AbdoolKarim'sand *et al* article '*Integration of Antiretroviral Therapy with Tuberculosis Treatment*'. The content, structure, strengths and limitations of the article were construed and dissected. The article has shared to a better understanding amongst the HIV fraternity, of the pros and cons of early and late initiation of ART in a TB–HIV Co-infected patient at different CD 4 levels. It is an accessible, easier to read, well researched and highly credible. It truly contemplates that integrating antiretroviral therapy (ART) with tuberculosis treatment reduces mortality though the timing for the initiation of ART during tuberculosis treatment remains uncertain. This article is being recommended for medical experts especially, the HIV care providers.

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