The role of antiretroviral therapy in reducing TB incidence and mortality in high HIV-TB burden countries

Anthony D Harries[1,2*], Ajay MV Kumar[1,3], Nang Thu Thu Kyaw[1,4], Nguyen Binh Hoa[1,5], Kudakwashe C Takarinda[1,6], Rony Zachariah[7]

[1]*International Union against Tuberculosis and Lung Disease, Paris, France*

[2]*London School of Hygiene and Tropical Medicine, Keppel Street, London, UK*

[3]*International Union Against Tuberculosis and Lung Disease, South-East Asia Regional Office, New Delhi, India*

[4]*International Union Against Tuberculosis and Lung Disease, Myanmar Country Office, Mandalay, Myanmar*

[5]*National Tuberculosis Control Programme, Hanoi, Vietnam*

[6]*AIDS and TB Department, Ministry of Health and Child Care, Harare, Zimbabwe*

[7]*Medecins Sans Frontieres, Medical Department, Operational Research Unit, Brussels Operational Centre, Luxembourg City, Luxembourg*

ARTICLE INFO

ABSTRACT

With the adoption of the new Sustainable Development Goals in 2016, all countries have committed to end the tuberculosis (TB) epidemic by 2030, defined as dramatic reductions in TB incidence and mortality combined with zero TB-induced catastrophic costs for families. This paper explores how antiretroviral therapy (ART) in high HIV-TB burden countries may help in reducing TB incidence and mortality and thus contribute to the ambitious goal of ending TB. ART in people living with HIV has a potent TB preventive effect, with this being most apparent in those with the most advanced immunodeficiency. Early ART also significantly reduces the risk of TB, and with new World Health Organization guidance released in 2015 about initiating ART in all persons living with HIV irrespective of CD4 count, there is the potential for enormous benefit at the population level. Already, several countries with high HIV-TB burdens have seen dramatic declines in TB case notification rates since ART scale up started in 2004. In patients already diagnosed with HIV-associated TB, mortality can be significantly decreased by ART, especially if started within 2–8 weeks of anti-TB treatment. The benefits of ART on TB incidence and TB mortality can be further augmented respectively by the addition of isoniazid preventive therapy and cotrimoxazole preventive therapy. These interventions must be effectively implemented and scaled up in order to end the TB epidemic by 2030.

1. Introduction

Despite steady progress in the implementation of the global "DOTS" and subsequently the "Stop TB" strategy since 1995, tuberculosis (TB) remains an enormous global public health challenge. Between 2000 and 2014, there was an overall 18% reduction in global TB incidence rates, but the total number of new cases in 2014 was still estimated at 9.6 million[1]. TB mortality has also fallen by 47% since 1990, with nearly all the improvement taking place since 2000 when the Millennium Development Goals were launched. But again, TB still kills too many people; the number of deaths due to TB was estimated at 1.5 million in 2014[1].

About 1.2 million people worldwide were thought to develop HIV-associated TB in 2014, and there were nearly 400 000 HIV-associated TB deaths[1]. The African region is the most affected by HIV-associated TB (the estimated number in 2014 being 870 000 or 73% of the global total). The South-East Asian Region and the Western Pacific together account for 240 000 cases of HIV-associated TB (20% of the global total) with India, Indonesia, Myanmar, Thailand, China and Vietnam accounting for the majority[1].

The next fifteen year period from 2016 to 2030 ushers in the new era of the Sustainable Development Goals[2]. In signing up to these

goals, all countries have committed to ending the TB epidemic by 2030, defined as dramatic reductions in TB incidence and mortality combined with zero TB-induced catastrophic costs for families (Table 1). This paper explores how antiretroviral therapy (ART) in high HIV-TB burden countries may help in reducing TB incidence and mortality and thus contribute to the ambitious goal of ending TB.

2. HIV/AIDS and the scale up of ART

The estimated numbers of people globally living with HIV/AIDS and the trends in scale up of ART each year are provided by the Joint United Nations Programme on HIV and AIDS (UNAIDS)[3]. By December 2014, there were 36.9 million people living with HIV/AIDS globally, 93% of whom were adults. In that year, 2.0 million people were newly infected with HIV and 1.2 million people died from HIV/AIDS, both of these estimates being slightly lower than those in the previous year. Sub-Saharan Africa continues to bear the brunt of this epidemic with about 70% of the disease burden residing in that region[3].

Despite the huge burden of infection and disease, the response to the global HIV epidemic has been remarkable, especially the public health scale up of ART. By the end of 2014, there were 14.9 million people globally receiving ART, representing 40% of people living with HIV[4]. By mid-2015, this number had reached 15.8 million. In sub-Saharan Africa, the region with the heaviest burden of HIV/AIDS, there has been excellent progress, especially in the eastern and southern regions of the continent, with 10.7 million people on ART by the end of 2014, representing 41% of all people living with HIV[4].

3. ART to decrease TB incidence

3.1. At the individual level

HIV is the most important risk factor for the development of TB in persons infected with *Mycobacterium tuberculosis* (MTB). HIV targets the host cell-mediated immune response to MTB[5], and, as a result, the risk of TB increases 2–3 times within the first two years after HIV seroconversion and continues to rise as the CD4 cell counts decrease[6]. HIV-infected individuals with MTB infection have an average annual risk of developing TB of approximately 10% per year, with the risk heavily dependent on the degree of immune deficiency, the amount of MTB transmission in the community and the prevailing socio-economic conditions[7,8]. Those with advanced immunodeficiency have an increasing risk of extra-pulmonary, disseminated and smear-negative TB. This pattern of TB is difficult

to diagnose in most health care facilities in resource-poor settings where HIV-TB flourishes and is associated with high mortality, much of which is not recognised or identified during life[9].

ART reverses the immune dysfunction associated with HIV. With initiation of ART, there is rapid functional recovery of mycobacteria-specific immune responses which results in enhanced capacity to restrict mycobacterial growth[10,11]. As a result, ART has a potent TB preventive effect. A systematic review and meta-analysis of 11 studies from 2002 to 2011 showed that ART was associated with a 65% reduction in TB incidence across all baseline CD4 counts in people living with HIV[12]. The effects of ART were stronger in those with more advanced HIV infection or with the lowest CD4 cell counts, but were also apparent in patients with CD4 counts > 350 cells/μL.

More recent studies have highlighted the TB preventive benefits of early start of ART and have also pointed out that delays in ART initiation when CD4 cell counts have dropped < 200 cells/μL can result in long-term immune dysfunction and persistent increased risk for TB[13,14]. The evidence of benefits in early ART initiation has been further strengthened by results from two randomised controlled studies published in 2015 (INSIGHT START and TEMPRANO)[15,16]. The INSIGHT START trial showed that early ART initiation in asymptomatic HIV-positive patients with CD4 counts > 500 cells/μL compared with deferred initiation until the CD4 count had decreased to 350 cells/μL was associated with a 57% reduction in risk of death, a serious AIDS-related event or a serious non-AIDS-related event, including TB[15]. TEMPRANO was a multicentre, randomized, 2-by-2 factorial design trial conducted in Cote d'Ivoire on patients with a CD4 cell count of < 800 cells/μL and meeting no criteria for starting ART according to the most recent World Health Organization (WHO) guidelines at enrolment[16]. Four groups were allocated to either immediate start of ART or deferred ART until WHO criteria for starting ART were met, and each group was also randomized to isoniazid preventive therapy (IPT) for 6 months or placebo. Early ART initiation was associated with a 44% lower risk of death or severe HIV-related illness (including TB) compared with ART initiated according to prevailing WHO criteria at the time, with IPT adding significantly to the individual benefit[16].

3.2. At the programmatic level

The data on individual patients are further supported by mathematical models that predict the enormous benefit that early ART initiation might have on TB prevention at the population level. Using data from the Southern African HIV/AIDS epidemic, a strategy of universal and annual HIV testing of adults with immediate start of ART in those diagnosed HIV-positive might be

Table 1

The End TB Strategy.

Indicators	Milestones		Targets	
	2020	2025	SDG 2030	End TB 2035
Reduced TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduced TB incidence compared with 2015 (%)	20% (< 85/100 000)	50% (< 55/100 000)	80% (< 20/100 000)	90% (< 10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

SDG: Sustainable Development Goals. Adapted from reference 2.

expected to halve the incidence of HIV-associated TB within a 5 year period[17].

At the programme level, despite people living with HIV routinely initiating ART at low CD4 counts, it has also been shown in Malawi and Swaziland that when ART coverage in the HIV-infected populations reaches a high level, TB case notification rates decrease[18-21]. In Malawi, for example, TB case notifications have declined from a peak of 28 234 in 2003 to 17 723 in 2014 (a 37% decline from 2003)[21]. The most significant declines in TB cases in Malawi and Swaziland were observed in patients with smear-negative pulmonary TB, a disease type strongly associated with HIV, and in Malawi significant declines were also documented in patients with recurrent TB, which is also strongly associated with HIV. In Malawi, while the decline in HIV-associated TB was of the order of 30% or more, there was also a 10% decline in HIV-negative TB[19]. This may be due to the overall decrease in HIV-associated TB in the community which in turn might have led to reduced community transmission of MTB and thus fewer cases of TB in the HIV uninfected population.

3.3. The need to consider IPT in addition to ART

While the data on ART in preventing TB are encouraging, ART on its own does not do the job adequately. At the laboratory level, long-term recovery of TB-specific immune function is incomplete on ART[10]. At the individual patient level, the beneficial TB preventive effects increase with length of time on ART and with ART-induced immune recovery, but the risk of TB never decreases to levels seen in patients without HIV-infection in the same community[22]. Additional interventions are therefore needed and IPT should be considered. Accumulated evidence suggests that IPT given at a daily dose of 300 mg for 6 months reduces the overall risk of TB in people living with HIV by 33%, with the protective effect largely seen in those with a positive tuberculin skin test[23].

Data from Botswana[24,25], Brazil[26], South Africa[27], and Ethiopia[28] suggest that sequential or concurrent use of ART and IPT results in additive effects in reducing the risk of active TB. This evidence has been further strengthened by two randomised controlled studies. The first, a placebo-controlled study in South Africa showed that IPT given for 12 months to people living with HIV and ART significantly reduced the risk of active TB by 37%, with the greatest benefit being observed in the first year[29]. Second, the TEMPRANO study confirmed the synergistic benefit of adding IPT to ART[16].

These data suggest that IPT is a useful addition to ART in preventing TB in high TB transmission settings, but further work is needed on safety, duration of IPT and how best to initiate and manage the two forms of treatment together.

4. ART to decrease TB mortality

4.1. The start and timing of ART

Case fatality rates are several times higher in patients with HIV-associated TB compared with those who have just TB alone[30].

ART administered to those with HIV-associated TB results in excellent immunological and virological responses and a reduction in mortality risk of 64%–95%[8,31]. HIV testing is the gateway to integrated care, but in 2014 only 51% of notified TB cases globally had a documented HIV test, the figure being highest in the Africa Region at 79% and low in the South-East Asian and Western Pacific Regions at 45% and 40% respectively[1]. The coverage of ART for notified TB cases known to be co-infected with HIV was 77% globally for the same year, with the African, South-East Asian and Western Pacific Regions being at 77%, 85% and 68% respectively.

The issue of optimal timing of ART in relation to start of anti-TB treatment in those known to have HIV-associated TB was clarified several years ago by three randomised controlled studies: CAMELIA, STRIDE and SAPIT[32-34]. While all three trials were slightly different, collectively one clear message emerged, namely, that earlier initiation of ART saves lives in HIV-infected patients with TB. The benefits were particularly evident for those with CD4 cell counts < 50 cells/μL in whom the risk of AIDS or death was minimised by starting ART within the first 2–4 weeks of TB treatment. One exception is in HIV-infected patients with TB meningitis in whom early ART is not associated with improved survival, and this may be because of the devastating effects of the immune reconstitution inflammatory syndrome within the confined space of the central nervous system[35]. These data have informed the 2013 WHO Guidelines on timing of ART for adults and children with TB. The recommendations currently are: i) ART be started in all HIV-infected TB patients, including those with drug-resistant TB, irrespective of CD4 count; ii) ART be initiated within the first eight weeks of anti-TB treatment, and in those with profound immunosuppression (such as CD4 counts < 50 cells/μL), ART be initiated within the first two weeks[36].

4.2. The need to consider cotrimoxazole preventive therapy (CPT) with ART

In 1999, a randomised controlled trial in Cote d'Ivoire found that the administration of trimethoprim-sulfamethoxazole (cotrimoxazole - CPT) to adults with HIV-associated TB substantially reduced severe clinical events and mortality[37]. This seminal study paved the way for a number of observational and randomised studies to assess efficacy, effectiveness and safety of CPT especially in sub-Saharan Africa. A recent systematic review and meta-analysis summarises current knowledge about the use of CPT in HIV-infected adults[38], and this was used for the formulation of the updated WHO recommendations on CPT in 2014[39]. In summary, across all global regions, CPT reduces death by 60% when started with ART in HIV-infected patients at CD4 counts ≤ 350 cells/μL. In Africa, CPT started without ART in patients with CD4 counts > 350 cells/μL reduces the overall risk of death and the risk of malaria. In Africa, the continuation of CPT after ART-induced recovery of CD4 cell counts > 350 cells/μL is associated with reduced hospital admission and reduced rates of malaria, pneumonia and diarrhoea. This suggests that in countries with a high burden of infectious diseases, CPT should be initiated before or with ART regardless of the CD4 count and should be continued

indefinitely.

5. Conclusion

In high HIV-TB burden countries, ART can play a significant role in helping to achieve the ambitious End TB targets of reduced TB incidence and mortality. In 2014, UNAIDS with support from WHO, released new 90-90-90 treatment targets for HIV[40]. These targets specify that by 2020, 90% of individuals living with HIV will know their HIV status, 90% of people with diagnosed HIV infection will receive sustained ART and 90% of those on ART will be virally suppressed. If this three-part strategy is achieved, it is estimated that nearly three quarters of all people living with HIV will be taking treatment and virally suppressed by 2020. Modelling studies suggest that this outcome will enable the world to end the AIDS epidemic by 2030 (defined as 90% decrease in HIV/AIDS incidence, 90% decrease in premature death and 90% decrease in new HIV infections)[41]. Achieving these targets will be crucial in the progress towards ending TB.

In people living with HIV/AIDS, widespread coverage and early start of ART are likely to significantly reduce TB case notification rates in both HIV-positive and HIV-negative persons. The recent WHO guidance launched on 30th September, 2015[41], recommending that ART be initiated in everyone living with HIV at any CD4 count should facilitate global scale up of ART and at a much earlier stage of immunosuppression than is currently the case. These recommendations will form part of the revised consolidated guidelines on the use of antiretroviral drugs to treat and prevent HIV infection which will be published by WHO in 2016.

A reduced incidence of TB will in itself reduce TB-related mortality, but this effect can be augmented by ensuring that all patients with HIV-associated TB are diagnosed early and started on ART, preferably within eight weeks of initiating anti-TB treatment. IPT and CPT can add significantly to the beneficial effects of ART by respectively helping to decrease TB incidence and HIV-associated mortality[42]. ART will work only through knowledge of HIV status, so the "*sine qua non*" is the provision of HIV testing and counselling to ensure that everyone with HIV knows that they are infected.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

References

[1] World Health Organization. Global tuberculosis report 2015. Geneva: World Health Organization; 2015. [Online] Available from: http:// apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf [Accessed on 24th February, 2016]

[2] World Health Organization. The End TB Strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2015. [Online] Available from: http://www. who.int/tb/post2015_TBstrategy.pdf [Accessed on 24th February, 2016]

[3] UNAIDS. Core epidemiology slides. Geneva: UNAIDS; 2015. [Online] Available from: http://www.unaids.org/en/resources/ documents/2015/20150714_coreepidemiologyslides_ppt [Accessed on 24th February, 2016]

[4] World Health Organization. Global health sector response to HIV, 2000-2015: focus on innovations in Africa. Geneva: World Health Organization; 2015. [Online] Available from: http://www.who.int/ hiv/pub/progressreports/2015-progress-report/en/ [Accessed on 24th February, 2016]

[5] Lawn SD, Butera ST, Shinnick TM. Tuberculosis unleashed: the impact of human immunodeficiency virus infection on the host granulomatous response to *Mycobacterium tuberculosis*. *Microbes Infect* 2002; **4**: 635-46.

[6] Holmes CB, Wood R, Badri M, Zilber S, Wang B, Maartens G, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; **42**: 464-9.

[7] Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009-21.

[8] Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? *Int J Tuberc Lung Dis* 2011; **15**: 571-81.

[9] Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS* 2015; **29**: 1987-2002.

[10] Lawn SD, Bekker LG, Wood R. How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. *AIDS* 2005; **19**: 1113-24.

[11] Kampmann B, Tena-Coki GN, Nicol MP, Levin M, Eley B. Reconstitution of antimycobacterial immune responses in HIV-infected children receiving HAART. *AIDS* 2006; **20**: 1011-8.

[12] Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Med* 2012; **9**: e1001270.

[13] Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, Eron J, Chen YQ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis* 2014; **14**: 281-90.

[14] Collins SE, Jean Juste MA, Koenig SP, Secours R, Ocheretina O, Bernard D, et al. CD4 deficit and tuberculosis risk persist with delayed antiretroviral therapy: 5-year data from CIPRA HT-001. *Int J Tuberc Lung Dis* 2015; **19**: 50-7.

[15] INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin

F, Emery S, Grund B, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795-807.

[16] TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808-22.

[17] Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. *Proc Nat Acad Sci U S A* 2010; **107**: 19485-9.

[18] Zachariah R, Bemelmans M, Akesson A, Gomani P, Phiri K, Isake B, et al. Reduced tuberculosis case notification associated with scaling up antiretroviral treatment in rural Malawi. *Int J Tuberc Lung Dis* 2011; **15**: 933-7.

[19] Kanyerere H, Mganga A, Harries AD, Tayler-Smith K, Jahn A, Chimbwandira FM, et al. Decline in national tuberculosis notifications with national scale-up of antiretroviral therapy in Malawi. *Public Health Action* 2014; **4**: 113-5.

[20] Haumba S, Dlamini T, Calnan M, Ghazaryan V, Smith-Arthur AE, Preko P, et al. Declining tuberculosis notification trend associated with strengthened and expanded HIV care in Swaziland. *Public Health Action* 2015; **5**: 103-5.

[21] Kanyerere H, Harries AD, Tayler-Smith K, Jahn A, Zachariah R, Chimbwandira FM, et al. The rise and fall of tuberculosis in Malawi: associations with HIV infection and antiretroviral therapy. *Trop Med Int Health* 2016; **21**: 101-7.

[22] Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: comparison with rates in the community. *PLoS One* 2012; **7**: e34156.

[23] Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV-infected persons. *Cochrane Database Syst Rev* 2010; (1): CD000171.

[24] Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377**: 1588-98.

[25] Samandari T, Agizew T, Nyirenda S, Tedla Z, Sibanda T, Mosimaneotsile B, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. *AIDS* 2015; **29**: 351-9.

[26] Golub JE, Saraceni V, Cavalcante SC, Pacheco AG, Moulton LH, King BS, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS* 2007; **21**: 1441-8.

[27] Golub JE, Pronyk P, Mohapi L, Thsabangu N, Moshabela M, Struthers H, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS* 2009; **23**: 631-6.

[28] Yirdaw KD, Jerene D, Gashu Z, Edginton ME, Kumar AM, Letamo Y, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. *PLoS One* 2014; **9**: e104557.

[29] Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent

tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; **384**: 682-90.

[30] Mukadi YD, Maher D, Harries AD. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001; **15**: 143-52.

[31] Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R, et al. The HIV-associated tuberculosis epidemic – when will we act? *Lancet* 2010; **375**: 1906-19.

[32] Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011; **365**: 1471-81.

[33] Havlir DV, Kendall MA, Ive P, Kumwenda J, Swindells S, Qasba SS, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011; **365**: 1482-91.

[34] Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med* 2011; **365**: 1492-501.

[35] Török ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis* 2011; **52**: 1374-83.

[36] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013. [Online] Available from: http://www. who.int/hiv/pub/guidelines/arv2013/download/en/ [Accessed on 24th February, 2016]

[37] Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999; **353**: 1469-75.

[38] Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, et al. Co-trimoxazole prophylaxis in adults, including pregnant women with HIV: a systematic review and meta-analysis. *Lancet HIV* 2015; **2**: e137-50.

[39] World Health Organization. Guidelines on post-exposure prophylaxis for HIV and use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Geneva: World Health Organization; 2014. [Online] Available from: http://www. who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en/ [Accessed on 24th February, 2016]

[40] UNAIDS. 90-90-90 - An ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS; 2014. [Online] Available from: http://www.unaids.org/en/resources/documents/2014/90-90-90 [Accessed on 24th February, 2016]

[41] World Health Organization. Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015. [Online] Available from: http://www.who. int/hiv/pub/guidelines/earlyrelease-arv/en/ [Accessed on 24th February, 2016]

[42] Harries AD, Lawn SD, Suthar AB, Granich R. Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. *Lancet Infect Dis* 2015; **15**: 1492-6.