HIV research in Indonesia, needs and opportunities: an update of knowledge and identification of research gaps

Wesley de Jong, Matthijs Raadsen, Musofa Rusli, Tri Pudy Asmarawati, Charles Boucher, Rob Gruters, Marco Goeijenbier, Eric van Gorp, Usman Hadi

Submitted.

ABSTRACT

Indonesia is behind in achieving the UNAIDS 2020 90-90-90 goals, as in 2018 close to 50% of HIV infected individuals were aware of their status and 17% used antiretroviral treatment (ART). The World Health Organization has specified a HIV continuum of services cascade, in which several key elements of the local HIV epidemic translate to preventive actions, diagnosis, accessibility of care and treatment. The needs to contain the HIV epidemic in Indonesia are different from Western countries. Therefore, based on data of research conducted in Indonesia, we have studied these key elements and we have identified research gaps that could promote future advances and potentiate improved control of the local HIV epidemic. An abundance of cross-sectional studies provide insight to the local epidemic, access to healthcare, effectiveness of ART and comorbidities. These studies are mainly focused on high risk groups and refrain from studying the epidemic in the general population. Only few have prospectively investigated the number of HIV infected individuals that are able to retain long-term treatment and virological suppression. Similar, other epidemiological data and baseline resistance is only sparse available, which hampers the formulation of new research questions and input for models that study interventions to contain the local HIV epidemic. The effects of a recently implemented nationwide health insurance are not yet clear, and together with the evolution of medical research over the past years in Indonesia, this might provide several unique opportunities to conduct phase 1 to 4 studies, study PrEP effectiveness and perform community science using social media.

INTRODUCTION

UNAIDS data for the archipelago Indonesia shows that of 270 million inhabitants, 640.000 people were living with HIV in 2018. Only 51% of HIV infected individuals were aware of their status and 17% used antiretroviral treatment (ART) (1). Low to middle-income countries, such as Indonesia, are characterized by a high number of HIV related deaths (2). The former shows that Indonesia is behind in achieving the ambitious UNAIDS 2020 90-90-90 goals (3). In June 2016, the World Health Organization published its global health sector strategy on HIV 2016-2021, which specifies a so-called HIV cascade that starts with reaching people at-risk for HIV infection with prevention and testing programs. The cascade then leads to having HIV positive persons on treatment, have them virologically suppressed and keep them in continuous care. This cascade must be achieved through a "continuum of services" that consists of prevention, diagnostics, care accessibility, treatment and permanent care. In this regard, scientific knowledge of several key aspects of the local HIV epidemic is essential to support policy making. Surveilling available scientific data also identifies research possibilities that could promote future advances in achieving the 90-90-90 goals and continuum of services. Based on the continuum of services (4), we have translated this to the following focus areas in research:

1. The local rate of HIV transmission and its main driving factors: know your epidemic (WHO). To target efforts for prevention and testing, it is essential to obtain knowledge of the epidemiology, routes of transmission, key populations at risk by demographics such as age, sex and geography.
2. Factors affecting access to test-and-treat and healthcare in general. To achieve the goal equitable access to HIV care, research plays an important role in identifying the barriers that exist between HIV positives and the healthcare system.
3. The effectiveness and outcomes of ART and related interventions such as therapy adherence, virological failure, ART resistance and pharmacokinetics. Evaluation of health interventions are crucial for continuous improvement of HIV care. Interventions that have proven effective in Western countries may not accomplish similar success in Indonesia due to differences in population settings and dynamics or genetic makeup.
4. The comorbidities experienced by people living with HIV in Indonesia. As more Indonesian HIV positives are started on ART, their life-expectancy will increase and their health care needs will evolve. Anticipating these needs is crucial to minimize disability, morbidity and mortality of HIV patients on long-term antiretroviral treatment.

This review provides the reader with an overview of the scientific literature regarding HIV in Indonesia in the era of ART. By analyzing the current state of scientific knowledge on the aforementioned four domains regarding HIV in Indonesia, our goal is to identify knowledge gaps that would potentiate future study in order to further prepare for the UNAIDS 2030 goals.

METHODS

A PUBMED/MEDLINE search was performed using keywords HIV and Indonesia on September 9th, 2019. Two authors (W.J., M.R.) independently selected relevant English written literature on studies conducted in adults, that were published from 1999 up till 2019 based on title/abstract. Available data were screened for relevance and categorized by subject and methodology as introduced above and detailed in Supplementary data 1. The number of available studies available from 2009 up till 2019 are grouped in the categories as introduced above and displayed in Figure 1. The authors selected a number of key papers for more in-depth discussion in the following paragraphs. For background information, we accessed Ministry of Health, Republic of Indonesia (MoH-RI) and World Health Organization (WHO) information at September 10th, 2019. We retrieved clinical trial information from both clinicaltrials.gov and centerwatch.com, using keyword HIV and study-sites in Indonesia, on September 10th, 2019.

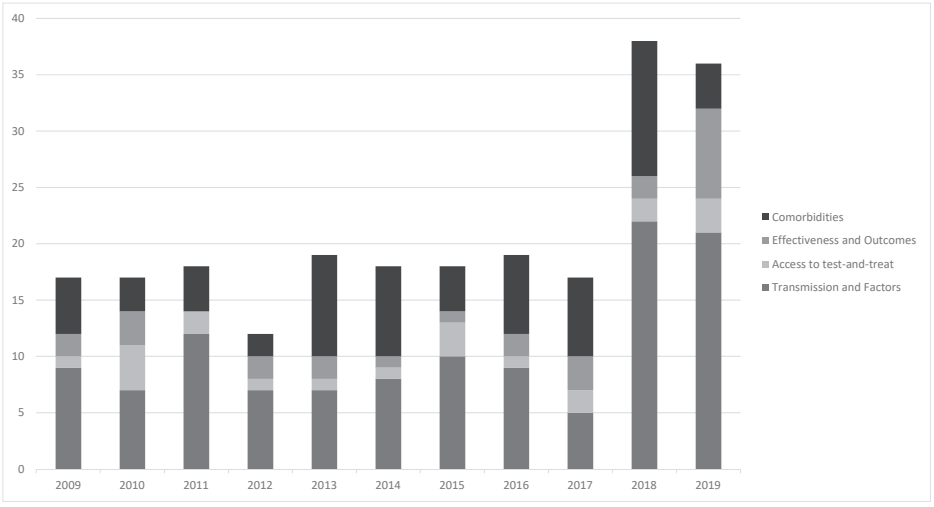

Figure 1. HIV research Indonesia: available publications
Absolute number of available publications categorized per: Local rate of HIV transmission and its main driving factors (Transmission and Factors), Factors affecting access to test-and-treat and healthcare in general (Access to test-and-treat), The effectiviness and outcomes of antiretroviral treatment and related interventions (Effectiveness and Outcomes), Comorbidities experienced (Comborbidities). Data based on PubMed search dated 9 September 2019 (refer to Methods section). * data reported until 9 September 2019

Overall availability of data

As shown in Figure 1, the mixture of topics in HIV related publications originating from Indonesian data shows a more or less stable pattern over the past decade until 2018. In 2018 and up till September 2019, the number of yearly publications has doubled in comparison to 2009-2017.

This is likely the result of increased efforts of the government to empower local researchers and establish international collaborations. The local rate of HIV transmission and its main driving factors are generally best represented in the studies conducted. These are mainly social sciences studies, which will not be discussed in detail here, as almost all have studied targeted small communities within the whole population.

Rates and drivers of HIV transmission

Understanding drivers of HIV transmission are crucial for setting up effective prevention programs as well as targeted intervention and treatment programs. The estimated prevalence of current HIV infections and incidence of new HIV infections is needed to direct the available resources or scale up for future perspectives. The first studies on HIV sero-prevalence in Indonesia are available starting from the mid 1990's. Both early and recent studies mainly focused on high-risk groups, such as men having sex with men (MSM) (5), transgender, sex workers and their clients (6-10), intravenous drug users (IVDU) (11, 12), prisoners (13, 14), military personnel (15) and people presenting to clinics suspect of a HIV infection (16-19). In these studies, HIV testing is often combined with screening for other sexually transmitted diseases (STD) and questionnaires to study attitudes, risk perception and risk behavior. The majority of studies available had a cross-sectional design of a single study group, and hence lack longitudinal data or a control group. The longest follow up duration was available from a study that was conducted among female sex workers in Western New Guinea. The authors reported a sharp increase in HIV incidence from 0.0% to 1.4% from the year 1998 to 2002 (9). A large study conducted in urban hospitals in Bali in 2003, reported no HIV infection in 2450 women screened (20), but a pooled analysis of sero-surveillance programs in Bali published in 2011 provides the most detailed analysis available for the overall epidemic to date. It describes trends of HIV transmission between the years 2000 and 2010. In addition, it reveals considerable heterogeneity between testing sites in terms of methodology, target groups tested and consistency of number of tested individuals. Some sites reported no testing during several years (21). It is suggested that introduction of HIV to Indonesia occurs mainly thru the Bali Island (22), possibly thru sex workers. Rahmalia and colleagues tried to gather insight in the proportion of females in the HIV overall epidemic, and prospectively enrolled over 2500 individuals in West-Java Island. They observed that intravenous drug usage (IVDU) contribution to HIV transmission in males is significantly higher than in women. From their data heterosexual transmission from male to female has become apparent as about a quarter of females were tested for HIV because of a positive partner (23). A cross-sectional study from Papua, which is considered to have the highest prevalence of HIV-1, found positive HIV antibodies in 1.27% of a small sample of 157 volunteers that were assumed healthy prior to study inclusion (24). No studies have been reported on blood bank samples or have performed sero-surveillance to determine the HIV prevalence in the general Indonesian population other than the surrogates mentioned above. Also, no recent studies investigating vertical (mother to child) transmission were found. More recently, molecular assays and whole genome sequencing, testing for HIV

clades and genotypes were introduced in studies (10, 14, 25-28). Such data is essential in cluster analysis of HIV cases as this could help to better understand HIV transmission in a country. This would help to set up prevention efforts with a better focus with respect to risk profile, culture, social-economic background and location (29). The Indonesian government currently still relies on health surveys to estimate the country's prevalence of HIV/AIDS, using self-reporting instead of nationwide testing and surveillance (30). According to the WHO global health sector strategy, building a comprehensive strategic information system for the HIV epidemic should be a fast-track action for countries. This requires a centrally coordinated effort to collect data in a standardized and sustained manner, to perform quality control and ensure that information is available rapidly to policymakers. Epidemiological data from Indonesia is available in the literature, but its collection still appears to be highly fragmented and inconsistent.

Factors affecting access to test-and-treat and healthcare in general

Multiple measures are needed to better control the HIV epidemic, and international guidelines should adjust to focused measures that reflect the local situation. The local situation in Indonesia is influenced for instance by stigma, faith and other human behavior such as governance. The following barriers in access to HIV care have been identified and studied: social stigma, lack of acceptance by target population, lack of available services, geographical isolation, financial barriers. Very few papers address these topics from a country-wide perspective. The process of adjusting international guidelines to local priorities was previously studied for the West-Java situation, based on a review of available governmental documents and putting out interviews (31, 32). The authors suggest that this approach, involving several local stakeholders, has helped in prioritizing actions to take control of the HIV epidemic. It seems useful to extend similar approaches to other provinces in Indonesia. Indonesia has introduced a compulsory national health insurance scheme, JKN, in 2014, expanding access to health insurance to more of its citizens. Historically, health insurance was only available to wealthier Indonesians, with only basic assistance for the poorest. Full implementation of the JKN was scheduled for the end of 2019 and an evaluation of its effects on healthcare equity is underway (33). Nowadays, ART should be available free of charge for the general public and is provided by the Indonesian Ministry of Health (34). The impact of this large scale health care reform for access to HIV care specifically could be substantial, but is yet to be evaluated. Performing long-term follow up studies of individuals who have been tested positive for HIV could provide insight into what proportion of them gains access to HIV care and what factors were of influence. As mentioned before, the abundance of social studies, is indicative of the interest in the complex human behavior and knowledge to be dealt with. The studies focus to either risk-groups or HIV confirmed cases e.g. HIV-positive MSM (35, 36), transgender (37) or IVDU (38). Remarkably, no studies have addressed the public opinion on HIV and HIV-testing uptake. In one manuscript it is recognized that a homophobic sentiment has increased social stigma and discrimination, which might keep MSM reluctant from accessing HIV services. This implies evitable continuation of HIV spread due to unprotected sex in MSM (39). Performance

and evaluation of commercial diagnostic assays to quantify HIV-1 viral loads was only studied by one group (40), and besides work published in 2012 on cost-saving HIV-1 quantitative RT-PCR alternatives (41), no recent data is available that has searched for alternatives to test for HIV. The most recent studies on costs of HIV prevention, care and treatment are mainly centered to data from West-Java and are performed by more or less the same research groups. It seems that the costs of HIV/AIDS interventions are unknown for the large part of Indonesia. Cost-effectiveness studies, modeling the local epidemic and interventions, could aid in targeting of available resources. This is for instance also suggested in a recent study of Verstraaten and colleagues. They have estimated the costs for several interventions such as condom distribution, education and care in Sexually Transmitted Infection clinics (42). Others have studied costs of providing ART and laboratory resources in relation to duration of several phases of HIV disease. The authors suggest to early initiate ART in those infected, not only based on HIV guidelines, but also to save on costs in future (43). Only one study has modeled costs of an intervention in the whole Indonesian population. Scaling up voluntary counselling and testing was found cost effective in reducing the overall population prevalence of HIV by 2030, but the authors are cautious in available budgeting (44). To date, no studies are performed on pre-exposure prophylaxis (PreP) of HIV, as PreP is not yet generally available in Indonesia. It might be helpful to perform cost-effectiveness studies based on the introduction of PreP, as promising method to constrain the HIV epidemic in targeted risk groups.

Effectiveness and outcomes of ART and interventions

Current international guidelines for HIV treatment state that, following immediate initiation of ART after HIV diagnosis, monitoring viral loads is recommended to detect treatment failure. In case viral load testing is not available, measuring CD4+ T-cell counts and clinical monitoring should be used as surrogate (45). Data on baseline HIV drug resistance is abundantly available from studies, but only from few places and mostly with a cross-sectional design. This includes for instance data from islands that are known tourism destinations, such as Kepulauan Riau (46) and Bali (47, 48). In Bali a sharp increase in baseline resistance was observed especially for sex workers and drug users (21). HIV-1 Circulating Recombinant Form (CRF) 01_AE, subtype A/E is considered the dominant subtype (28). This finding was later repeated in studies conducted with HIV infected individuals that were either treatment naïve or failed treatment. In some studies, it was suggested that there is no transmitted drug resistance (TDR) (47), though in contrast others provide strong evidence for emergence of TDR in their studies from West-Papua (49), which was later confirmed in West-Java (50-52). To better understand emerging TDR on a country level, data should be pooled, or routine diagnostics in case of (first-line) treatment regimen failure could be implemented. This is also suggested in the WHO action plan on HIV drug resistance (53) – especially in the light large-scale implementation of integrase inhibitors in middle income countries. Alternative assays to test for treatment failure were performed, and it was suggested that total lymphocyte count might serve as alternative to relative costly CD4+ T cell count assays (54) in

models predicting HIV related mortality. Pharmacological studies are relevant to understand drug metabolism and interactions in a given population. These are limited available in Indonesia. As example, the impact of rifampicin treatment for tuberculosis on plasma efavirenz concentrations was explored and it is was found that there was a higher proportion of patients with a detectable viral load in those receiving rifampicin (55). The authors suggest that larger studies are needed. Polymorphisms for CYP2B6, one of the most polymorphic CYP genes in human, were studied and it was found to impact efavirenz plasma levels (56). Similar studies were conducted on rifampicin and nevirapine, which has showed significant lower levels of nevirapine in those treated with rifampicin, though nevirapine levels were still within therapeutic range (57). Such studies are of continued importance as most clinical trials were mostly performed in Western countries, where the ethnic makeup of the population does not represent the Indonesian population. In addition, the occurrence of coinfections, such as tuberculosis, are relatively rare. Factors such as genetic polymorphisms, body mass, co-medication and diet are known to influence the pharmacokinetics and pharmacodynamics of ART and modify the effectiveness of these drugs in the Indonesian population. The former is also relevant in the future emergence of dolutegravir containing regimens in Indonesia and the high number of tuberculosis co-infections in Indonesia (58). Outcomes of those in HIV care, and on treatment were only subject of a few prospective studies. The most important study on clinical HIV care in Indonesia is that of Januraga and colleagues. During a one-year period they have recruited and followed several key populations, comprising a total of 831 MSM, female sex workers and IVDU at four study sites throughout Indonesia. They found that participants were more likely to start ART in case they were enrolled in facilities that offered both testing and treatment, compared to facilities that only offered testing. After a year, just over half were retained in care and remarkably, 43% of the female sex workers was lost to follow-up (59) The findings are comparable to other studies, for instance a study investigating 8430 person-years over a 7-year period in Bandung (60). In this regard, a study from Bali has found that in the period 2006-2014, annual mortality rate in the cohort of HIV-1 infected patients attending medical care was 10% (61). These findings provide important ground for future research and interventions to keep HIV infected individuals on therapy. Similarly, the TREAT Asia HIV/AIDS Observational Database (TAHOD) (62) and INAPROACTIVE (63) initiative will provide prospectively collected data from those in HIV care. Such approaches have proven their value in understanding the local HIV epidemic, as for instance is clearly seen in the Dutch ATHENA cohort. Data collection of HIV infected individuals in the Netherlands has started over two decades ago (64).

Co-infections and comorbidities

Co-infections refer to the opportunistic infections acquired by patients with AIDS, due to their severely immunocompromised status, or non-opportunistic infections which share transmission routes with HIV such as hepatitis A,B and C. The term comorbidity is used to describe non-infectious illnesses, the occurrence of which relates to HIV infection and/or ART. All available studies on co-infections and comorbidities are overviewed in Table 1. The majority of recent data

on co-infections is available from cohorts of M. tuberculosis for which the majority of studies has a prospective design (65-72) (N=21) or Hepatitis C co-infections (73-80) (N=8). For Hepatitis B, the most recent study was published in 2019 in a cohort of female prisoners (76), and the most recent study performed in HIV infected patients visiting outpatient clinics dates from 2015 (81). Sexually transmitted diseases were subject of 8 studies. Central nervous system (CNS) infections are also studied in more detail. For instance studies on etiology and outcomes of brain infections are relevant, as these greatly contribute to HIV related deaths (82-85). In addition, a ten-year cohort study of CNS infections has specifically studied tuberculous meningitis (86) and another study has prospectively collected data of over 600 patients with tuberculous meningitis (87). Most research on co-infections in Indonesian HIV patients has focused on organisms that are typically also implicated in the HIV infected population in Western countries, such as toxoplasma, Cryptococcus, tuberculosis, STD's, viral hepatitis, etc. Remarkably, no studies examining Pneumocystis jiroveci pneumonia were found, while this is considered a common opportunistic infection in persons with HIV (88). Some studies have also examined the disease burden of specific pathogens that are highly endemic in Indonesia, such as Blastocystis, Cyclospora and Entamoeba. We only found one case report on histoplasmosis infection in a patient with HIV, despite the fact that this is a known opportunistic pathogen that is endemic in Indonesia (89) This may simply reflect a low disease burden, but it could also mean this disease has been neglected in Indonesia. Histoplasmin skin test positivity has been tested as high as 63.4% in Indonesia, however these surveys were conducted in the 1950's and very little recent data is available (90). It is important to determine the incidence of histoplasmosis in HIV infected individuals in endemic regions, since itraconazole prophylaxis could be considered if the incidence is high.

Studies performed in Western countries show that HIV positive patients on long-term ART are much more susceptible to develop hypertension, obesity and metabolic syndrome, along with their related complications (91). A cross-sectional study performed by Rodriguez-Fernandez et al in 2016 examined patient records of a predominantly male mining community in Papua in order to determine the level of comorbidity between infectious and non-infectious disease. The study found frequent comorbidity of noninfectious disease with malaria and TB, but none with HIV/AIDS (92). This could be due to the relatively high disease burden of malaria on Papua Indonesia relative to the number of HIV/AIDS cases. The results do highlight the public health challenge faced by rapidly developing economies of incomplete elimination of "old health" infectious diseases combined with the emergence of "new health" non-infectious diseases related to increased wealth, such as cardiovascular and pulmonary disease. A more in depth prospective cohort study specifically in different Indonesian HIV positive populations could reveal substantial comorbidities between HIV and these wealth-related diseases that are missed by cross sectional surveys of the general population. As test-and-treat will evolve in Indonesia, it will be important to monitor for similar effects in the Indonesian population. So far, most studies have used retrospective and cross-sectional designs. These are the least demanding in terms of cost and labor, but come

with significant methodological limitations. For this, prospective study designs are the preferred method.

Research gaps, needs and possible opportunities for HIV research

The archipelagic layout, a continuous economic growth (93) and faith and stigma are just some of the main challenges in controlling the HIV epidemic in Indonesia. The interplay of factors to reach the UNAIDS 2030 goals and to improve the quality of life of people living with HIV in Indonesia is complex. We suggest that scientific studies could not only help to fill gaps in knowledge, but additionally, rationally designed prospective or modelling studies would aid in understanding the effectiveness of interventions in the HIV epidemic in Indonesia. The needs to contain the HIV epidemic in Indonesia are different from Western countries, and efforts should therefore be made to translate international findings to local priorities with help of local stakeholders, or repeat scientific studies in Indonesia. In general, it seems first and foremost important to alleviate any physical and emotional barriers to test-and-treatment facilities. The recent implementation of nationwide health insurance is an important milestone, though the effects on the HIV epidemic are not yet clear. Stigma and homophobic sentiments need urgent attention as the number of new HIV infections in MSM is still high. Test-and-treat is important from both the patients perspective, as well as from a public health perspective, to control individual quality of life, co-infections and to halt the ongoing HIV transmission. As discussed before, well designed routine collection of clinical data and outcomes is needed, preferably targeted around risk-groups or treatment facilities. This is found useful in other countries, and based on previous studies conducted in Indonesia, also locally. It is likely to contribute to the understanding of the dynamics of the HIV epidemic. With the data in hand, one could formulate new research questions, both retrospectively and prospectively. Ultimately all patients failing on therapy should be included in a cohort study on nationwide drug resistance as this would help to develop future directions in HIV treatment. There is also a need to extend research to the general population, as current research is only limited to high risk groups. These high risk groups are of known importance in the HIV epidemic, but for instance might also contribute to HIV emergence in the non-risk group population. No recent scientific data is available on HIV in blood donors, while from other infectious diseases, such as Hepatitis B, this was found useful in estimating the epidemic. We found limited studies on alternative and more affordable options to test for HIV. Such studies might not only reduce costs of HIV testing, but might also increase HIV testing uptake by reducing financial barriers that people face. There is a lack of phase 1-4 clinical intervention studies. As outlined before, the local genotype and co-infections might influence treatment efficacy and clinical outcomes. Given an increasing number of publications from Indonesian researchers over recent years, it seems that clinical research has greatly evolved in Indonesia. Historically, pharmaceutical companies and other sources of funding have made it possible for Western countries to conduct research and to set-up new research lines. In this regard, Indonesia, habiting over 260 million people, might be an interesting market for pharmaceutical companies, non-governmental organizations and other

funders to invest in healthcare advances. Future advances in HIV research include the introduction of PreP, HIV cure and increasing use of social media and community science. Locally, this could translate to a halt or constrain of HIV transmission in high risk groups if PreP would become available to a fair price. HIV cure research would be especially interesting for the high number of newly diagnosed HIV infections. Social media and community science could help in rapidly spread information to distant areas and to collect research data from the whole country with just a tap on a mobile device. The increasing amount of available studies on HIV in Indonesia not only is indicative of interest in HIV research, it also implies readiness to combat future challenges by deploying research and exploring other possibilities to contain the HIV epidemic.

REFERENCES – MAIN ARTICLE

1. UNAIDS. UNAIDS DATA 2018: UNAIDS; 2018 [Available from: https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf.
2. Harries AD, Suthar AB, Takarinda KC, Tweya H, Kyaw NT, Tayler-Smith K, et al. Ending the HIV/AIDS epidemic in low- and middle-income countries by 2030: is it possible? F1000Res. 2016;5:2328.
3. UNAIDS. 90–90–90 - An ambitious treatment target to help end the AIDS epidemic: UNAIDS; 2017 [updated 01 JANUARY 2017. Available from: https://www.unaids.org/en/resources/documents/2017/90-90-90.
4. WHO. GLOBAL HEALTH SECTOR STRATEGY ON HIV 2016–2021 TOWARDS ENDING AIDS: WHO; 2016 [updated 01 June 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/246178/WHO-HIV-2016.05-eng.pdf;jsessionid=0B775C5962093252837B1CA7954DB3BC?sequence=1.
5. Pisani E, Girault P, Gultom M, Sukartini N, Kumalawati J, Jazan S, et al. HIV, syphilis infection, and sexual practices among transgenders, male sex workers, and other men who have sex with men in Jakarta, Indonesia. Sex Transm Infect. 2004;80(6):536-40.
6. Joesoef MR, Linnan M, Barakbah Y, Idajadi A, Kambodji A, Schulz K. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. Int J STD AIDS. 1997;8(9):576-80.
7. Ford K, Wirawan DN, Reed BD, Muliawan P, Sutarga M. AIDS and STD knowledge, condom use and HIV/STD infection among female sex workers in Bali, Indonesia. AIDS Care. 2000;12(5):523-34.
8. Sugihantono A, Slidell M, Syaifudin A, Pratjojo H, Utami IM, Sadjimin T, et al. Syphilis and HIV prevalence among commercial sex workers in Central Java, Indonesia: risk-taking behavior and attitudes that may potentiate a wider epidemic. AIDS Patient Care STDS. 2003;17(11):595-600.
9. Silitonga N, Davies SC, Kaldor J, Wignall S, Okoseray M. Prevalence over time and risk factors for sexually transmissible infections among newly-arrived female sex workers in Timika, Indonesia. Sex Health. 2011;8(1):61-4.
10. Kotaki T, Khairunisa SQ, Sukartiningrum SD, Arfijanto MV, Utsumi T, Normalina I, et al. High prevalence of HIV-1 CRF01_AE viruses among female commercial sex workers residing in Surabaya, Indonesia. PLoS One. 2013;8(12):e82645.
11. Yona S, Ismail R, Nurachmah E, Levy J, Norr K. Gaining a "normal life": HIV-positive Indonesian female injection drug users in drug recovery. J Ethn Subst Abuse. 2019:1-18.
12. Stoicescu C, Cluver LD, Spreckelsen TF, Mahanani MM, Ameilia R. Intimate partner violence and receptive syringe sharing among women who inject drugs in Indonesia: A respondent-driven sampling study. Int J Drug Policy. 2019;63:1-11.
13. Nelwan EJ, Van Crevel R, Alisjahbana B, Indrati AK, Dwiyana RF, Nuralam N, et al. Human immunodeficiency virus, hepatitis B and hepatitis C in an Indonesian prison: prevalence, risk factors and implications of HIV screening. Trop Med Int Health. 2010;15(12):1491-8.
14. Prasetyo AA, Dirgahayu P, Sari Y, Hudiyono H, Kageyama S. Molecular epidemiology of HIV, HBV, HCV, and HTLV-1/2 in drug abuser inmates in central Javan prisons, Indonesia. J Infect Dev Ctries. 2013;7(6):453-67.
15. Porter KR, Mascola JR, Hupudio H, Ewing D, VanCott TC, Anthony RL, et al. Genetic, antigenic and serologic characterization of human immunodeficiency virus type 1 from Indonesia. J Acquir Immune Defic Syndr Hum Retrovirol. 1997;14(1):1-6.
16. Davies SC, Madjid B, Pardohudoyo S, Wiraguna AA, Patten JH, Upadisari LP. Prevalence of sexually transmissible infections (STI) among male patients with STI in Denpasar and Makassar, Indonesia: are symptoms of urethritis sufficient to guide syndromic treatment? Sex Health. 2007;4(3):213-5.

17. Hinduan ZR, Kesumah N, Iskandar Z, van Crevel R, Alisjahbana B, Hospers HJ. Characteristics of subjects counseled and tested for HIV in an Indonesian hospital; factors associated with HIV-status and CD4 cell-count. Acta Med Indones. 2009;41 Suppl 1:12-7.
18. Pontororing GJ, Kenangalem E, Lolong DB, Waramori G, Sandjaja, Tjitra E, et al. The burden and treatment of HIV in tuberculosis patients in Papua Province, Indonesia: a prospective observational study. BMC Infect Dis. 2010;10:362.
19. Guy R, Mustikawati DE, Wijaksono DB, Nugraihini N, Priohutomo S, Silitonga N, et al. Voluntary counselling and testing sites as a source of sentinel information on HIV prevalence in a concentrated epidemic: a pilot project from Indonesia. Int J STD AIDS. 2011;22(9):505-11.
20. Surya IG, Kornia K, Suwardewa TG, Mulyanto, Tsuda F, Mishiro S. Serological markers of hepatitis B, C, and E viruses and human immunodeficiency virus type-1 infections in pregnant women in Bali, Indonesia. J Med Virol. 2005;75(4):499-503.
21. Januraga PP, Wulandari LP, Muliawan P, Sawitri S, Causer L, Wirawan DN, et al. Sharply rising prevalence of HIV infection in Bali: a critical assessment of the surveillance data. Int J STD AIDS. 2013;24(8):633-7.
22. Ueda S, Witaningrum AM, Khairunisa SQ, Kotaki T, Nasronudin, Kameoka M. Genetic Diversity and Drug Resistance of HIV-1 Circulating in North Sulawesi, Indonesia. AIDS Res Hum Retroviruses. 2019;35(4):407-13.
23. Rahmalia A, Wisaksana R, Meijerink H, Indrati AR, Alisjahbana B, Roeleveld N, et al. Women with HIV in Indonesia: are they bridging a concentrated epidemic to the wider community? BMC Res Notes. 2015;8:757.
24. Yunifiar MQ, Kotaki T, Witaningrum AM, Khairunisa SQ, Indriati DW, Meilani M, et al. Sero- and Molecular Epidemiology of HIV-1 in Papua Province, Indonesia. Acta Med Indones. 2017;49(3):205-14.
25. Foley B, Donegan E, Silitonga N, Wignall FS, Busch MP, Delwart EL. Importation of multiple HIV type 1 strains into West Papua, Indonesia (Irian Jaya). AIDS Res Hum Retroviruses. 2001;17(17):1655-9.
26. Sahbandar IN, Takahashi K, Djoerban Z, Firmansyah I, Naganawa S, Motomura K, et al. Current HIV type 1 molecular epidemiology profile and identification of unique recombinant forms in Jakarta, Indonesia. AIDS Res Hum Retroviruses. 2009;25(7):637-46.
27. SahBandar IN, Takahashi K, Motomura K, Djoerban Z, Firmansyah I, Kitamura K, et al. The indonesian variants of CRF33_01B: Near-full length sequence analysis. AIDS Res Hum Retroviruses. 2011;27(1):97-102.
28. Merati TP, Ryan CE, Spelmen T, Wirawan DN, Bakta IM, Otto B, et al. CRF01_AE dominates the HIV-1 epidemic in Indonesia. Sex Health. 2012;9(5):414-21.
29. Grabowski MK, Herbeck JT, Poon AFY. Genetic Cluster Analysis for HIV Prevention. Curr HIV/AIDS Rep. 2018;15(2):182-9.
30. MoH-RI. Indonesia Dempographic and Health Survey 2017 2017 [updated September 2018. Available from: https://www.aidsdatahub.org/sites/default/files/publication/DHS_2017_Indonesia_2018.pdf.
31. Tromp N, Prawiranegara R, Subhan Riparev H, Siregar A, Sunjaya D, Baltussen R. Priority setting in HIV/AIDS control in West Java Indonesia: an evaluation based on the accountability for reasonableness framework. Health Policy Plan. 2015;30(3):345-55.
32. Tromp N, Prawiranegara R, Siregar A, Wisaksana R, Pinxten L, Pinxten J, et al. Translating international HIV treatment guidelines into local priorities in Indonesia. Trop Med Int Health. 2018;23(3):279-94.
33. Wiseman V, Thabrany H, Asante A, Haemmerli M, Kosen S, Gilson L, et al. An evaluation of health systems equity in Indonesia: study protocol. Int J Equity Health. 2018;17(1):138.
34. UNAIDS. Indonesia report NCPI (National Commitments and Policies Instrument) 2013–2014: UNAIDS; 2013 [updated 2013. Available from: http://files.unaids.org/en/dataanalysis/knowyourresponse/ncpi/2014countries/Indonesia%20NCPI%202013.pdf.

35. Victoryna F, Yona S, Waluyo A. The relationship between stigma, family acceptance, peer support and stress level among HIV-positive men who have sex with men (MSM) in Medan, North Sumatera, Indonesia. Enferm Clin. 2019.
36. Fitriyani RA, Waluyo A. Family acceptance, peer support, and HIV serostatus disclosure of MSM-PLWHA in Medan, Indonesia. Enferm Clin. 2019.
37. Fauk NK, Merry MS, Putra S, Sigilipoe MA, Crutzen R, Mwanri L. Perceptions among transgender women of factors associated with the access to HIV/AIDS-related health services in Yogyakarta, Indonesia. PLoS One. 2019;14(8):e0221013.
38. Go VF, Hershow RB, Kiriazova T, Sarasvita R, Bui Q, Latkin CA, et al. Client and Provider Perspectives on Antiretroviral Treatment Uptake and Adherence Among People Who Inject Drugs in Indonesia, Ukraine and Vietnam: HPTN 074. AIDS Behav. 2019;23(4):1084-93.
39. Bagcchi S. Homophobic sentiment hinders Indonesia's anti-HIV drive. Lancet Infect Dis. 2016;16(12):1339.
40. Kosasih AS, Sugiarto C, Hayuanta HH, Juhaendi R, Setiawan L. Performance Evaluation of the Bioneer AccuPower(R) HIV-1 Quantitative RT-PCR kit: Comparison with the Roche COBAS(R) AmpliPrep/COBAS TaqMan(R) HIV-1 Test Ver.2.0 for Quantification of HIV-1 Viral Load in Indonesia. Asian Pac J Allergy Immunol. 2018;36(2):120-5.
41. Fibriani A, Farah N, Kusumadewi I, Pas SD, van Crevel R, van der Ven A, et al. Low cost HIV-1 quantitative RT-PCR assay in resource-limited settings: improvement and implementation. J Virol Methods. 2012;185(1):118-23.
42. Verstraaten EJM, Beeren FMM, Janssen JLC, Kemper S, Siregar AYM, Tromp N, et al. Comparative Cost Analysis of Four Interventions to Prevent HIV Transmission in Bandung, Indonesia. Acta Med Indones. 2017;49(3):236-42.
43. Siregar AY, Tromp N, Komarudin D, Wisaksana R, van Crevel R, van der Ven A, et al. Costs of HIV/AIDS treatment in Indonesia by time of treatment and stage of disease. BMC Health Serv Res. 2015;15:440.
44. Tromp N, Siregar A, Leuwol B, Komarudin D, van der Ven A, van Crevel R, et al. Cost-effectiveness of scaling up voluntary counselling and testing in West-Java, Indonesia. Acta Med Indones. 2013;45(1):17-25.
45. WHO. WHAT'S NEW IN TREATMENT MONITORING: VIRAL LOAD AND CD4 TESTING: WHO; 2017 [updated July 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/255891/WHO-HIV-2017.22-eng.pdf;jsessionid=15F3DF97126359EACA97266A96BFB346?sequence=1.
46. Khairunisa SQ, Ueda S, Witaningrum AM, Yunifiar Matondang MQ, Indriati DW, Kotaki T, et al. Genotypic Characterization of Human Immunodeficiency Virus Type 1 Prevalent in Kepulauan Riau, Indonesia. AIDS Res Hum Retroviruses. 2018;34(6):555-60.
47. Budayanti NS, Merati TP, Bela B, Mahardika GN. Molecular Antiretroviral Resistance Markers of Human Immunodeficiency Virus-1 of CRF01_AE Subtype in Bali, Indonesia. Curr HIV Res. 2018;16(5):374-82.
48. Megasari NLA, Oktafiani D, Ana EF, Ueda S, Kotaki T, Nasronudin, et al. Genotypic Characterization of Human Immunodeficiency Virus Type 1 Isolated from Antiretroviral Treatment-Experienced Individuals in Buleleng Regency, Bali, Indonesia. AIDS Res Hum Retroviruses. 2019;35(8):769-74.
49. Witaningrum AM, Kotaki T, Khairunisa SQ, Yunifiar MM, Indriati DW, Bramanthi R, et al. Genotypic Characterization of Human Immunodeficiency Virus Type 1 Derived from Antiretroviral Therapy-Naive Individuals Residing in Sorong, West Papua. AIDS Res Hum Retroviruses. 2016;32(8):812-7.
50. Kotaki T, Khairunisa SQ, Witaningrum AM, M MQY, Sukartiningrum SD, Diansyah MN, et al. HIV-1 transmitted drug resistance mutations among antiretroviral therapy-Naive individuals in Surabaya, Indonesia. AIDS Res Ther. 2015;12:5.

51. Khairunisa SQ, Kotaki T, Witaningrum AM, Yunifiar MM, Sukartiningrum SD, Nasronudin, et al. Appearance of drug resistance-associated mutations in human immunodeficiency virus type 1 protease and reverse transcriptase derived from drug-treated Indonesian patients. AIDS Res Hum Retroviruses. 2015;31(2):255-9.
52. Kotaki T, Khairunisa SQ, Sukartiningrum SD, Witaningrum AM, Rusli M, Diansyah MN, et al. Detection of drug resistance-associated mutations in human immunodeficiency virus type 1 integrase derived from drug-naive individuals in Surabaya, Indonesia. AIDS Res Hum Retroviruses. 2014;30(5):489-92.
53. WHO. GLOBAL ACTION PLAN ON HIV DRUG RESISTANCE 2017-2021: WHO; 2017 [updated July 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/255883/9789241512848-eng.pdf?sequence=1.
54. Oudenhoven HP, Meijerink H, Wisaksana R, Oetojo S, Indrati A, van der Ven AJ, et al. Total lymphocyte count is a good marker for HIV-related mortality and can be used as a tool for starting HIV treatment in a resource-limited setting. Trop Med Int Health. 2011;16(11):1372-9.
55. Mariana N, Purwantyastuti, Instiaty, Rusli A. Efavirenz Plasma Concentrations and HIV Viral Load in HIV/AIDS-tuberculosis Infection Patients Treated with Rifampicin. Acta Med Indones. 2016;48(1):10-6.
56. Zakeri S, Amiri N, Pirahmadi S, Dinparast Djadid N. Genetic variability of CYP2B6 polymorphisms in southeast Iranian population: implications for malaria and HIV/AIDS treatment. Arch Iran Med. 2014;17(10):685-91.
57. Nafrialdi, Nugroho AW, Yunihastuti E, Wiria MS. Influence of rifampicin on nevirapine plasma concentration in HIV-TB coinfected patients. Acta Med Indones. 2012;44(2):135-9.
58. Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-Based Antiretroviral Therapy for Patients Co-Infected with Tuberculosis and Hiv: A Multicenter, Noncomparative, Open-Label, Randomized Trial. Clin Infect Dis. 2019.
59. Januraga PP, Reekie J, Mulyani T, Lestari BW, Iskandar S, Wisaksana R, et al. The cascade of HIV care among key populations in Indonesia: a prospective cohort study. Lancet HIV. 2018;5(10):e560-e8.
60. Rahmalia A, Price MH, Hartantri Y, Alisjahbana B, Wisaksana R, van Crevel R, et al. Are there differences in HIV retention in care between female and male patients in Indonesia? A multi-state analysis of a retrospective cohort study. PLoS One. 2019;14(6):e0218781.
61. Utami S, Sawitri AAS, Wulandari LPL, Artawan Eka Putra IWG, Astuti PAS, Wirawan DN, et al. Mortality among people living with HIV on antiretroviral treatment in Bali, Indonesia: incidence and predictors. Int J STD AIDS. 2017;28(12):1199-207.
62. amfAR. TREAT Asia HIV/AIDS Observational Database: amfAR; 2008 [updated 2008. Available from: https://www.amfar.org/around-the-world/treat-asia/research-and-treatment/treat-asia-hiv-aids-observational-database/.
63. ClinicalTrials.gov. HIV Infection and Risk Related Coinfections/Comorbidities in Indonesia (INAPRO-ACTIVE): ClinicalTrials.gov; 2018 [updated 10-09-2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03663920.
64. Boender TS, Smit C, Sighem AV, Bezemer D, Ester CJ, Zaheri S, et al. AIDS Therapy Evaluation in the Netherlands (ATHENA) national observational HIV cohort: cohort profile. BMJ Open. 2018;8(9):e022516.
65. Rewata L, Rutherford M, Apriani L, Janssen W, Rahmadi A, Parwati I, et al. Improving diagnosis of pulmonary tuberculosis among HIV/AIDS patients: literature review and experience in a teaching hospital in Indonesia. Acta Med Indones. 2009;41 Suppl 1:57-64.
66. Sumatoh HR, Oliver BG, Kumar M, Elliott JH, Vonthanak S, Vun MC, et al. Mycobacterial antibody levels and immune restoration disease in HIV patients treated in South East Asia. Biomark Med. 2011;5(6):847-53.

67. Saktiawati AMI, Subronto YW, Stienstra Y, Sumardi, Supit F, van der Werf TS. Sensitivity and specificity of routine diagnostic work-up for tuberculosis in lung clinics in Yogyakarta, Indonesia: a cohort study. BMC Public Health. 2019;19(1):363.
68. Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, Alisjahbana B, et al. Implementation of LED fluorescence microscopy for diagnosis of pulmonary and HIV-associated tuberculosis in a hospital setting in Indonesia. PLoS One. 2013;8(4):e61727.
69. Santoso P, Soeroto AY, Juniati R, Hartantri Y, Wisaksana R, Alisjabana B, et al. Improving Diagnostic of Pulmonary Tuberculosis in HIV Patients by Bronchoscopy: A Cross Sectional Study. Acta Med Indones. 2017;49(4):330-5.
70. Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, Maguire G, et al. Tuberculosis outcomes in Papua, Indonesia: the relationship with different body mass index characteristics between papuan and non-Papuan ethnic groups. PLoS One. 2013;8(9):e76077.
71. Meijerink H, Wisaksana R, Lestari M, Meilana I, Chaidir L, van der Ven AJ, et al. Active and latent tuberculosis among HIV-positive injecting drug users in Indonesia. J Int AIDS Soc. 2015;18:19317.
72. Meijerink H, Tacke S, Indrati A, Wisaksana R, Alisjahbana B, van der Ven A. Decreased whole blood RNA expression of cathelicidin in HIV-infected heroin users in Bandung, Indonesia. Viral Immunol. 2014;27(10):551-5.
73. Yunihastuti E, Lee S, Gani RA, Saraswati H, Sundaru H, Lesmana LA, et al. Antibody and markers of T-cell activation illuminate the pathogenesis of HCV immune restoration disease in HIV/HCV co-infected patients commencing ART. Clin Immunol. 2011;139(1):32-9.
74. Gani RA, Yunihastuti E, Krisnuhoni E, Saraswati H, Djauzi S, Lesmana LA, et al. Periportal CD4+ cell infiltration increases in HIV/hepatitis C virus-coinfected patients commencing ART, whereas CD8+ cells clear from the liver. J Infect Dis. 2014;210(3):405-9.
75. Juniastuti, Utsumi T, Nasronudin, Alimsardjono L, Amin M, Adianti M, et al. High rate of seronegative HCV infection in HIV-positive patients. Biomed Rep. 2014;2(1):79-84.
76. Arends RM, Nelwan EJ, Soediro R, van Crevel R, Alisjahbana B, Pohan HT, et al. Associations between impulsivity, risk behavior and HIV, HBV, HCV and syphilis seroprevalence among female prisoners in Indonesia: A cross-sectional study. PLoS One. 2019;14(2):e0207970.
77. Durier N, Yunihastuti E, Ruxrungtham K, Kinh NV, Kamarulzaman A, Boettiger D, et al. Chronic hepatitis C infection and liver disease in HIV-coinfected patients in Asia. J Viral Hepat. 2017;24(3):187-96.
78. Kurniawan J, Gani RA, Hasan I, Sulaiman AS, Lesmana CRA, Jasirwan COM, et al. Comparative efficacy of sofosbuvir-ribavirin versus sofosbuvir-daclatasvir for treatment of chronic hepatitis C in an area with limited NS5A inhibitor availability. Indian J Gastroenterol. 2018;37(6):520-5.
79. Hadikusumo AA, Utsumi T, Amin M, Khairunisa SQ, Istimagfirah A, Wahyuni RM, et al. High Rates of Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus Infections and Uncommon HBV Genotype/Subtype and HCV Subtype Distributions among Transgender Individuals in Surabaya, Indonesia. Jpn J Infect Dis. 2016;69(6):493-9.
80. Anggorowati N, Yano Y, Heriyanto DS, Rinonce HT, Utsumi T, Mulya DP, et al. Clinical and virological characteristics of hepatitis B or C virus co-infection with HIV in Indonesian patients. J Med Virol. 2012;84(6):857-65.
81. Yano Y, Utsumi T, Lusida MI, Hayashi Y. Hepatitis B virus infection in Indonesia. World J Gastroenterol. 2015;21(38):10714-20.
82. Imran D, Estiasari R, Maharani K, Sucipto, Lestari DC, Yunus RE, et al. Presentation, etiology, and outcome of brain infections in an Indonesian hospital: A cohort study. Neurol Clin Pract. 2018;8(5):379-88.

83. Donovan J, Phu NH, Mai NTH, Dung LT, Imran D, Burhan E, et al. Adjunctive dexamethasone for the treatment of HIV-infected adults with tuberculous meningitis (ACT HIV): Study protocol for a randomised controlled trial. Wellcome Open Res. 2018;3:31.
84. Ganiem AR, Indrati AR, Wisaksana R, Meijerink H, van der Ven A, Alisjahbana B, et al. Asymptomatic cryptococcal antigenemia is associated with mortality among HIV-positive patients in Indonesia. J Int AIDS Soc. 2014;17:18821.
85. Ganiem AR, Parwati I, Wisaksana R, van der Zanden A, van de Beek D, Sturm P, et al. The effect of HIV infection on adult meningitis in Indonesia: a prospective cohort study. Aids. 2009;23(17):2309-16.
86. Chaidir L, Annisa J, Dian S, Parwati I, Alisjahbana A, Purnama F, et al. Microbiological diagnosis of adult tuberculous meningitis in a ten-year cohort in Indonesia. Diagn Microbiol Infect Dis. 2018;91(1):42-6.
87. van Laarhoven A, Dian S, Ruesen C, Hayati E, Damen M, Annisa J, et al. Clinical Parameters, Routine Inflammatory Markers, and LTA4H Genotype as Predictors of Mortality Among 608 Patients With Tuberculous Meningitis in Indonesia. J Infect Dis. 2017;215(7):1029-39.
88. Low A, Gavriilidis G, Larke N, MR BL, Drouin O, Stover J, et al. Incidence of Opportunistic Infections and the Impact of Antiretroviral Therapy Among HIV-Infected Adults in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016;62(12):1595-603.
89. Anggorowati N, Sulistyaningsih RC, Ghozali A, Subronto YW. Disseminated Histoplasmosis in an Indonesian HIV-Positive Patient: A Case Diagnosed by Fine Needle Aspiration Cytology. Acta Med Indones. 2017;49(4):360-2.
90. Baker J, Setianingrum F, Wahyuningsih R, Denning DW. Mapping histoplasmosis in South East Asia - implications for diagnosis in AIDS. Emerg Microbes Infect. 2019;8(1):1139-45.
91. Lagathu C, Bereziat V, Gorwood J, Fellahi S, Bastard JP, Vigouroux C, et al. Metabolic complications affecting adipose tissue, lipid and glucose metabolism associated with HIV antiretroviral treatment. Expert Opin Drug Saf. 2019;18(9):829-40.
92. Rodriguez-Fernandez R, Ng N, Susilo D, Prawira J, Bangs MJ, Amiya RM. The double burden of disease among mining workers in Papua, Indonesia: at the crossroads between Old and New health paradigms. BMC Public Health. 2016;16:951.
93. UNDP. Indonesia: UNDP; 2019 [updated 2019. Available from: https://www.id.undp.org/content/indonesia/en/home/countryinfo.html.

Table 1

	Cross-sectional	Retrospective	Prospective	Total
Co-infections				
Opportunistic				
Intestinal parasites *	3 (1-3)	-	1 (4)	4
Toxoplasma	3 (5-7)	-	2 (8-9)	5
Mycobacteria	3 (10-12)	2 (13-14)	16 (9, 15-29)	21
Candida	1 (30)	-	1 (31)	3 (32) (Case report)
Cryptococcus	-	-	3 (9, 17, 33)	3
CMV	1 (6)	-	2 (9, 34)	3
HHV	1 (35)	-	-	1
Pneumocystis	-	-	-	-
Histoplasmosis	-	-	-	1 (36) (Case report)
VZV	-	-	1 (9)	1
Scabies	-	1 (37)	-	1
RSV	-	-	1 (38)	1
Molluscum contagiosum	1 (6)	1 (37)	-	2
Plasmodium	1 (29)	1 (39)	-	2
Streptococcus	2 (40-41)	-	-	2
Shared transmission route				
HBV	3 (7, 42-43)	1 (44)	-	4
HCV	4 (7, 43, 45, 46)	2 (44, 47)	2 (48, 49)	8
HDV	1 (7)	-	-	1
HTLV 1/2	1 (7)	-	-	1
GBV-C	2 (50-51)	-	-	2
STD #	4 (52-55)	1 (37)	3 (9, 56-57)	8
HPV	1 (58)	1 (37)	1 (57)	3
HSV 1/2	3 (55, 59, 60)	1 (37)	2 (9, 57)	6
Comorbidities				
CVD	4 (29, 61-63)	-	1 (64)	5
Metabolic syndrome	1 (29)	-	1 (16)	2
IRIS	-	-	2 (19, 48)	2
Malignancy	1 (29)	-	-	1
Lymphoma	-	-	1 (9)	1
Skin disorders	1 (65)	-	-	1
Bone disorders	4 (66-69)	-	-	4
Hematologic disorder	2 (70-71)	-	-	2
Neurological disorder	1 (72)	-	-	1
Ocular disorder	1 (6)	-	-	1
Pulmonary disorder	1 (29)	-	-	1
Drug abuse	1 (73)	1 (74)	-	2

CMV = Cytomegalovirus, HHV = Human Herpesvirus, NTM = nontuberculous mycobacteria, VZV = Varicella Zoster Virus, RSV = Respiratory Syncytial Virus, HBV = Hepatitis B Virus, HCV = Hepatitis C Virus, HDV = Hepatitis D Virus, HTLV = Human T-Lymphotropic Virus, HPV = Human Papilloma Virus HSV = Herpes Simplex Virus, CVD = Cardiovascular diseases, IRIS = Immune Reconstitution Inflammatory Syndrome.

** Ascaris, Blastocystis, Cyclospra, Cryptosporidium, Entamoeba, Giardia.)*

 # Syphilis, Chlamydia, Gonorrhoea, Trichomonas, Mycoplasma genitalum, Bacterial vaginosis

REFERENCES – TABLE 1

1. Kurniawan A, Karyadi T, Dwintasari SW, Sari IP, Yunihastuti E, Djauzi S, et al. Intestinal parasitic infections in HIV/AIDS patients presenting with diarrhoea in Jakarta, Indonesia. Trans R Soc Trop Med Hyg. 2009;103(9):892-8.
2. Kurniawan A, Dwintasari SW, Connelly L, Nichols RA, Yunihastuti E, Karyadi T, et al. Cryptosporidium species from human immunodeficiency-infected patients with chronic diarrhea in Jakarta, Indonesia. Ann Epidemiol. 2013;23(11):720-3.
3. Darlan DM, Rozi MF, Andriyani Y, Yulfi H, Saragih RH, Nerdy N. Cryptosporidium Sp. Findings and Its Symptomatology among Immunocompromised Patients. Open Access Maced J Med Sci. 2019;7(10):1567-71.
4. Idris NS, Dwipoerwantoro PG, Kurniawan A, Said M. Intestinal parasitic infection of immunocompromised children with diarrhoea: clinical profile and therapeutic response. J Infect Dev Ctries. 2010;4(5):309-17.
5. Konishi, Houki Y, Harano K, Mibawani RS, Marsudi D, Alibasah S, et al. High prevalence of antibody to Toxoplasma gondii among humans in Surabaya, Indonesia. Jpn J Infect Dis. 2000;53(6):238-41.
6. Lestari YD, Sitompul R, Edwar L, Djoerban Z. Ocular diseases among HIV/AIDS patients in Jakarta, Indonesia. Southeast Asian J Trop Med Public Health. 2013;44(1):62-71.
7. Sari Y, Haryati S, Raharjo I, Prasetyo AA. Toxoplasma and Viral Antibodies among Hiv Patients and Inmates in Central Java, Indonesia. Southeast Asian J Trop Med Public Health. 2015;46(6):977-85.
8. Ganiem AR, Dian S, Indriati A, Chaidir L, Wisaksana R, Sturm P, et al. Cerebral toxoplasmosis mimicking subacute meningitis in HIV-infected patients; a cohort study from Indonesia. PLoS Negl Trop Dis. 2013;7(1):e1994.
9. Imran D, Estiasari R, Maharani K, Sucipto, Lestari DC, Yunus RE, et al. Presentation, etiology, and outcome of brain infections in an Indonesian hospital: A cohort study. Neurol Clin Pract. 2018;8(5):379-88.
10. Fredy FC, Liwang F, Kurniawan R, Nasir AU. The correlation between CD4+ T-lymphocyte count and tuberculosis form in TB-HIV coinfected patients in Indonesia. Acta Med Indones. 2012;44(2):122-7.
11. Chaidir L, Parwati I, Annisa J, Muhsinin S, Meilana I, Alisjahbana B, et al. Implementation of LED fluorescence microscopy for diagnosis of pulmonary and HIV-associated tuberculosis in a hospital setting in Indonesia. PLoS One. 2013;8(4):e61727.
12. Santoso P, Soeroto AY, Juniati R, Hartantri Y, Wisaksana R, Alisjabana B, et al. Improving Diagnostic of Pulmonary Tuberculosis in HIV Patients by Bronchoscopy: A Cross Sectional Study. Acta Med Indones. 2017;49(4):330-5.
13. Ardian M, Meokbun E, Siburian L, Malonda E, Waramori G, Penttinen P, et al. A public-private partnership for TB control in Timika, Papua Province, Indonesia. Int J Tuberc Lung Dis. 2007;11(10):1101-7.
14. Sumantri S, Djoerban Z. Clinical manifestations and antiretroviral management of HIV/AIDS patients with tuberculosis co-infection in Kramat 128 Hospital. Acta Med Indones. 2008;40(3):117-23.
15. Kelly PM, Scott L, Krause VL. Tuberculosis in east timorese refugees: implications for health care needs in East Timor. Int J Tuberc Lung Dis. 2002;6(11):980-7.
16. Alisjahbana B, van Crevel R, Sahiratmadja E, den Heijer M, Maya A, Istriana E, et al. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. Int J Tuberc Lung Dis. 2006;10(6):696-700.
17. Ganiem AR, Parwati I, Wisaksana R, van der Zanden A, van de Beek D, Sturm P, et al. The effect of HIV infection on adult meningitis in Indonesia: a prospective cohort study. Aids. 2009;23(17):2309-16.

18. Rewata L, Rutherford M, Apriani L, Janssen W, Rahmadi A, Parwati I, et al. Improving diagnosis of pulmonary tuberculosis among HIV/AIDS patients: literature review and experience in a teaching hospital in Indonesia. Acta Med Indones. 2009;41 Suppl 1:57-64.
19. Sumatoh HR, Oliver BG, Kumar M, Elliott JH, Vonthanak S, Vun MC, et al. Mycobacterial antibody levels and immune restoration disease in HIV patients treated in South East Asia. Biomark Med. 2011;5(6):847-53.
20. Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, Maguire G, et al. Tuberculosis outcomes in Papua, Indonesia: the relationship with different body mass index characteristics between papuan and non-Papuan ethnic groups. PLoS One. 2013;8(9):e76077.
21. Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, et al. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. PLoS One. 2013;8(11):e80302.
22. Ruslami R, Ganiem AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, et al. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 2013;13(1):27-35.
23. Meijerink H, Wisaksana R, Lestari M, Meilana I, Chaidir L, van der Ven AJ, et al. Active and latent tuberculosis among HIV-positive injecting drug users in Indonesia. J Int AIDS Soc. 2015;18:19317.
24. van Laarhoven A, Dian S, Ruesen C, Hayati E, Damen M, Annisa J, et al. Clinical Parameters, Routine Inflammatory Markers, and LTA4H Genotype as Predictors of Mortality Among 608 Patients With Tuberculous Meningitis in Indonesia. J Infect Dis. 2017;215(7):1029-39.
25. Chaidir L, Annisa J, Dian S, Parwati I, Alisjahbana A, Purnama F, et al. Microbiological diagnosis of adult tuberculous meningitis in a ten-year cohort in Indonesia. Diagn Microbiol Infect Dis. 2018;91(1):42-6.
26. Donovan J, Phu NH, Mai NTH, Dung LT, Imran D, Burhan E, et al. Adjunctive dexamethasone for the treatment of HIV-infected adults with tuberculous meningitis (ACT HIV): Study protocol for a randomised controlled trial. Wellcome Open Res. 2018;3:31.
27. van Laarhoven A, Dian S, Aguirre-Gamboa R, Avila-Pacheco J, Ricano-Ponce I, Ruesen C, et al. Cerebral tryptophan metabolism and outcome of tuberculous meningitis: an observational cohort study. Lancet Infect Dis. 2018;18(5):526-35.
28. Saktiawati AMI, Subronto YW, Stienstra Y, Sumardi, Supit F, van der Werf TS. Sensitivity and specificity of routine diagnostic work-up for tuberculosis in lung clinics in Yogyakarta, Indonesia: a cohort study. BMC Public Health. 2019;19(1):363.
29. Rodriguez-Fernandez R, Ng N, Susilo D, Prawira J, Bangs MJ, Amiya RM. The double burden of disease among mining workers in Papua, Indonesia: at the crossroads between Old and New health paradigms. BMC Public Health. 2016;16:951.
30. Rosana Y, Yasmon A, Lestari DC. Overexpression and mutation as a genetic mechanism of fluconazole resistance in Candida albicans isolated from human immunodeficiency virus patients in Indonesia. J Med Microbiol. 2015;64(9):1046-52.
31. Wulandari EAT, Saraswati H, Adawiyah R, Djauzi S, Wahyuningsih R, Price P. Immunological and epidemiological factors affecting candidiasis in HIV patients beginning antiretroviral therapy in an Asian clinic. Arch Oral Biol. 2017;82:86-91.
32. Wahyuningsih R, SahBandar IN, Theelen B, Hagen F, Poot G, Meis JF, et al. Candida nivariensis isolated from an Indonesian human immunodeficiency virus-infected patient suffering from oropharyngeal candidiasis. J Clin Microbiol. 2008;46(1):388-91.
33. Ganiem AR, Indrati AR, Wisaksana R, Meijerink H, van der Ven A, Alisjahbana B, et al. Asymptomatic cryptococcal antigenemia is associated with mortality among HIV-positive patients in Indonesia. J Int AIDS Soc. 2014;17:18821.

34. Ariyanto IA, Estiasari R, Waters S, Wulandari EAT, Fernandez S, Lee S, et al. Active and Persistent Cytomegalovirus Infections Affect T Cells in Young Adult HIV Patients Commencing Antiretroviral Therapy. Viral Immunol. 2018;31(6):472-9.
35. Oktafiani D, Megasari NLA, Fitriana E, Nasronudin, Lusida MI, Soetjipto. Detection of Human Herpesvirus-8 Antigen in Hiv-Infected Patients in East Java, Indonesia. Afr J Infect Dis. 2018;12(2):43-6.
36. Anggorowati N, Sulistyaningsih RC, Ghozali A, Subronto YW. Disseminated Histoplasmosis in an Indonesian HIV-Positive Patient: A Case Diagnosed by Fine Needle Aspiration Cytology. Acta Med Indones. 2017;49(4):360-2.
37. Harnanti DV, Hidayati AN, Miftahussurur M. Concomitant Sexually Transmitted Diseases in Patients with Diagnosed Hiv/Aids: A Retrospective Study. Afr J Infect Dis. 2018;12(1 Suppl):83-9.
38. Robertson SE, Roca A, Alonso P, Simoes EA, Kartasasmita CB, Olaleye DO, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ. 2004;82(12):914-22.
39. Douglas NM, Pontororing GJ, Lampah DA, Yeo TW, Kenangalem E, Poespoprodjo JR, et al. Mortality attributable to Plasmodium vivax malaria: a clinical audit from Papua, Indonesia. BMC Med. 2014;12:217.
40. Safari D, Kurniati N, Waslia L, Khoeri MM, Putri T, Bogaert D, et al. Serotype distribution and antibiotic susceptibility of Streptococcus pneumoniae strains carried by children infected with human immunodeficiency virus. PLoS One. 2014;9(10):e110526.
41. Harimurti K, Saldi SR, Dewiasty E, Khoeri MM, Yunihastuti E, Putri T, et al. Nasopharyngeal carriage of Streptococcus pneumoniae in adults infected with human immunodeficiency virus in Jakarta, Indonesia. J Infect Public Health. 2016;9(5):633-8.
42. Fibriani A, Wisaksana R, Alisjahbana B, Indrati A, Schutten M, van Crevel R, et al. Hepatitis B virus prevalence, risk factors and genotype distribution in HIV infected patients from West Java, Indonesia. J Clin Virol. 2014;59(4):235-41.
43. Hadikusumo AA, Utsumi T, Amin M, Khairunisa SQ, Istimagfirah A, Wahyuni RM, et al. High Rates of Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus Infections and Uncommon HBV Genotype/Subtype and HCV Subtype Distributions among Transgender Individuals in Surabaya, Indonesia. Jpn J Infect Dis. 2016;69(6):493-9.
44. Anggorowati N, Yano Y, Heriyanto DS, Rinonce HT, Utsumi T, Mulya DP, et al. Clinical and virological characteristics of hepatitis B or C virus co-infection with HIV in Indonesian patients. J Med Virol. 2012;84(6):857-65.
45. Juniastuti, Utsumi T, Nasronudin, Alimsardjono L, Amin M, Adianti M, et al. High rate of seronegative HCV infection in HIV-positive patients. Biomed Rep. 2014;2(1):79-84.
46. Durier N, Yunihastuti E, Ruxrungtham K, Kinh NV, Kamarulzaman A, Boettiger D, et al. Chronic hepatitis C infection and liver disease in HIV-coinfected patients in Asia. J Viral Hepat. 2017;24(3):187-96.
47. Kurniawan J, Gani RA, Hasan I, Sulaiman AS, Lesmana CRA, Jasirwan COM, et al. Comparative efficacy of sofosbuvir-ribavirin versus sofosbuvir-daclatasvir for treatment of chronic hepatitis C in an area with limited NS5A inhibitor availability. Indian J Gastroenterol. 2018;37(6):520-5.
48. Yunihastuti E, Lee S, Gani RA, Saraswati H, Sundaru H, Lesmana LA, et al. Antibody and markers of T-cell activation illuminate the pathogenesis of HCV immune restoration disease in HIV/HCV co-infected patients commencing ART. Clin Immunol. 2011;139(1):32-9.
49. Gani RA, Yunihastuti E, Krisnuhoni E, Saraswati H, Djauzi S, Lesmana LA, et al. Periportal CD4+ cell infiltration increases in HIV/hepatitis C virus-coinfected patients commencing ART, whereas CD8+ cells clear from the liver. J Infect Dis. 2014;210(3):405-9.

50. Muerhoff AS, Dawson GJ, Desai SM. A previously unrecognized sixth genotype of GB virus C revealed by analysis of 5'-untranslated region sequences. J Med Virol. 2006;78(1):105-11.
51. Anggorowati N, Yano Y, Subronto YW, Utsumi T, Heriyanto DS, Mulya DP, et al. GB virus C infection in Indonesian HIV-positive patients. Microbiol Immunol. 2013;57(4):298-308.
52. Davies SC, Otto B, Partohudoyo S, Chrisnadarmani VA, Neilsen GA, Ciaffi L, et al. Sexually transmitted infections among female sex workers in Kupang, Indonesia: searching for a screening algorithm to detect cervical gonococcal and chlamydial infections. Sex Transm Dis. 2003;30(9):671-9.
53. Majid N, Bollen L, Morineau G, Daily SF, Mustikawati DE, Agus N, et al. Syphilis among female sex workers in Indonesia: need and opportunity for intervention. Sex Transm Infect. 2010;86(5):377-83.
54. Tanudyaya FK, Rahardjo E, Bollen LJ, Madjid N, Daili SF, Priohutomo S, et al. Prevalence of sexually transmitted infections and sexual risk behavior among female sex workers in nine provinces in Indonesia, 2005. Southeast Asian J Trop Med Public Health. 2010;41(2):463-73.
55. Mawu FO, Davies SC, McKechnie M, Sedyaningsih ER, Widihastuti A, Hillman RJ. Sexually transmissible infections among female sex workers in Manado, Indonesia, using a multiplex polymerase chain reaction-based reverse line blot assay. Sex Health. 2011;8(1):52-60.
56. Joesoef MR, Karundeng A, Runtupalit C, Moran JS, Lewis JS, Ryan CA. High rate of bacterial vaginosis among women with intrauterine devices in Manado, Indonesia. Contraception. 2001;64(3):169-72.
57. Ford K, Reed BD, Wirawan DN, Muliawan P, Sutarga M, Gregoire L. The Bali STD/AIDS study: human papillomavirus infection among female sex workers. Int J STD AIDS. 2003;14(10):681-7.
58. Somia IKA, Teeratakulpisarn N, Jeo WS, Yee IA, Pankam T, Nonenoy S, et al. Prevalence of and risk factors for anal high-risk HPV among HIV-negative and HIV-positive MSM and transgender women in three countries at South-East Asia. Medicine (Baltimore). 2018;97(10):e9898.
59. Davies SC, Taylor JA, Sedyaningsih-Mamahit ER, Gunawan S, Cunningham AL, Mindel A. Prevalence and risk factors for herpes simplex virus type 2 antibodies among low- and high-risk populations in Indonesia. Sex Transm Dis. 2007;34(3):132-8.
60. Wiraguna A, Andriani PI, Adiguna MS. Comparison of Plasma Zinc Levels Among HIV+ and HIV- Subjects Infected with Condyloma Acuminata. Asian Pac J Cancer Prev. 2019;20(3):943-9.
61. Idris NS, Cheung MM, Grobbee DE, Burgner D, Kurniati N, Djer MM, et al. Effects of paediatric HIV infection on electrical conduction of the heart. Open Heart. 2016;3(1):e000340.
62. Idris NS, Cheung MM, Grobbee DE, Burgner D, Kurniati N, Uiterwaal CS. Cardiac Effects of Antiretroviral-Naive versus Antiretroviral-Exposed HIV Infection in Children. PLoS One. 2016;11(1):e0146753.
63. Idris NS, Grobbee DE, Burgner D, Cheung MM, Kurniati N, Uiterwaal CS. Effects of paediatric HIV infection on childhood vasculature. Eur Heart J. 2016;37(48):3610-6.
64. Karim B, Wijaya IP, Rahmaniyah R, Ariyanto I, Waters S, Estiasari R, et al. Factors affecting affect cardiovascular health in Indonesian HIV patients beginning ART. AIDS Res Ther. 2017;14(1):52.
65. Dwiyana RF, Rowawi R, Lestari M, Alisjahbana B, van der Ven AJ, Djajakusumah TS. Skin disorders in HIV-infected patients from West Java. Acta Med Indones. 2009;41 Suppl 1:18-22.
66. Setiyohadi B, Mulansari NA, Sukmana N. Reduced bone mineral density and serum C-telopeptide concentration in HIV-infected patients in Cipto Mangunkusumo Hospital. Acta Med Indones. 2009;41(4):191-4.
67. Masyeni S, Utama S, Somia A, Widiana R, Merati TP. Factors influencing bone mineral density in ARV-naive patients at Sanglah Hospital, Bali. Acta Med Indones. 2013;45(3):175-9.
68. Sudjaritruk T, Bunupuradah T, Aurpibul L, Kosalaraksa P, Kurniati N, Prasitsuebsai W, et al. Hypovitaminosis D and hyperparathyroidism: effects on bone turnover and bone mineral density among perinatally HIV-infected adolescents. Aids. 2016;30(7):1059-67.

69. Sudjaritruk T, Bunupuradah T, Aurpibul L, Kosalaraksa P, Kurniati N, Prasitsuebsai W, et al. Adverse bone health and abnormal bone turnover among perinatally HIV-infected Asian adolescents with virological suppression. HIV Med. 2017;18(4):235-44.
70. Wisaksana R, Sumantri R, Indrati AR, Zwitser A, Jusuf H, de Mast Q, et al. Anemia and iron homeostasis in a cohort of HIV-infected patients in Indonesia. BMC Infect Dis. 2011;11:213.
71. Wahyuwibowo J, Harumsari S, Zulaikha ST, Suwondo A, Sofro MAU, Hadisaputro S. Age and CD4 count are dominant factors in the prediction of anaemia in Javanese HIV patients. Asia Pac J Clin Nutr. 2018;27(3):649-54.
72. Mawuntu AHP, Mahama CN, Khosama H, Estiasari R, Imran D. Early detection of peripheral neuropathy using stimulated skin wrinkling test in human immunodeficiency virus infected patients: A cross-sectional study. Medicine (Baltimore). 2018;97(30):e11526.
73. Meijerink H, Tacke S, Indrati A, Wisaksana R, Alisjahbana B, van der Ven A. Decreased whole blood RNA expression of cathelicidin in HIV-infected heroin users in Bandung, Indonesia. Viral Immunol. 2014;27(10):551-5.
74. Meijerink H, Wisaksana R, Iskandar S, den Heijer M, van der Ven AJ, Alisjahbana B, et al. Injecting drug use is associated with a more rapid CD4 cell decline among treatment naive HIV-positive patients in Indonesia. J Int AIDS Soc. 2014;17:18844.

Supplementary data 1

Classification of Available Literature

Literature was assigned to the following categories as described in 'Introduction' and 'Methods' section of the main manuscript, based on title/abstract. A single category was assigned per manuscript. Research that was not performed in Indonesia or in case the results had limited implications for Indonesia (i.e. single cases or cohort studies with a minor representation of Indonesian participants), were excluded from further review.

Categories *with criteria for classification*

1. **Local rate of HIV transmission and its main driving factors**

diagnostic assays for HIV; novel and/or surrogate biomarkers; epidemiological studies reporting incidence and/or prevalence; HIV genotyping / sequencing and drug resistance at baseline (transmitted resistance); current knowledge and behavior (not studying interventions that aim to change knowledge and behavior); studies on preventive or curative measures for HIV i.e. to change behavior; increase HIV testing uptake

2. **Factors affecting access to test-and-treat and healthcare in general**

estimated or real costs of HIV test-and-treat and/or interventions; economic burden in general; investigations of capacity and quality of health care and supporting systems; regulatory issues;

3. **The effectiveness and outcomes of antiretroviral treatment (ART) and related interventions in the Indonesian population such as therapy adherence, virological failure, ART resistance and pharmacokinetics**

pharmacological studies; outcomes on individuals on ART and therapy adherence; quality of life assessments of people living with HIV

4. **The comorbidities experienced by people living with HIV in Indonesia**

co-infections (acute and chronic) or co-morbidities reported in HIV-infected individuals (not: treatment outcomes); studies reporting infectious disease cohorts that included HIV testing (co-infection);