Review Article

Disparities in the Magnitude of Human Immunodeficiency Virus-related Opportunistic Infections Between High and Low/Middle-income Countries: Is Highly Active Antiretroviral Therapy Changing the Trend?

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Abstract

Opportunistic infections (OIs) cause significant morbidity/mortality in human immunodeficiency virus (HIV)-infected individuals globally. Disparities between high-income countries (HICs) and low/middle-income countries (LMICs) in the magnitude of HIV-related OIs in pre-highly active antiretroviral therapy (HAART) populations was reviewed, and HAART-induced decline in OIs was further compared between the two settings. Studies published in English from onset of HIV epidemic up to December 2013 were searched in PubMed, Google, Google Scholar, and African Journal online. An article was included if (a) the study was conducted in HIC or LMIC, (b) the age of the participants was ≥12 years, (c) the HAART status of the participants was stated, and (d) various types of OIs were investigated. In predominantly pre-HAART populations, the incidence and prevalence of overall HIV-related OIs in HIC ranged from 5.5 to 50.0 per 100 person-years (PY) and 27.4–56.7%, respectively. In LMIC, the respective overall incidence and prevalence of OIs were 12.2–93.9 per 100 PY and 32.0–77.7%. *Pneumocystis jirovecii* pneumonia, candidiasis, *Cytomegalovirus* disease, *Mycobacterium avium* complex disease, and Kaposi's sarcoma were the most frequent OIs in HICs while tuberculosis, candidiasis, chronic diarrhea, and cryptococcosis were predominant in LMICs. The introduction of HAART led to substantial reduction in the incidence of OIs with more impressive percentage decline in HICs (43–97%) compared to 30–79% in LMICs. Disparities in the magnitude of HIV-related OIs between HICs and LMICs are evident both in the pre-HAART and post-HAART era. Efforts to optimize HAART-induced decline in HIV-related OIs should become a global health priority irrespective of prevailing socioeconomic circumstances.

Keywords: Acquired immune deficiency syndrome, Disparities, High-income country, Highly active antiretroviral therapy, Human immunodeficiency virus, Low-income country, Middle-income country, Opportunistic infections

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Introduction

The human immunodeficiency virus (HIV) infection and its progression to the acquired immune deficiency syndrome (AIDS) have significantly affected the global health statistics over the past three decades. Globally, there are an estimated 35.3 million people living with HIV (PLHIV), and 2.3 million new HIV infections and 1.6 million AIDS deaths occur annually.[1] By far, the greatest impact of the disease has been in low- and middle-income countries (LMICs) where an estimated 90% of the global HIV-infected population live.[1]

The hallmark of HIV infection is immunosuppression which predisposes affected individuals to infections by unusual pathogens referred to as opportunistic infections (OIs). OIs constitute a major cause of morbidity and mortality in PLHIV, globally.[2-6] Over the three decades of the HIV epidemic, HIV-related OIs commonly reported in various populations include *Pneumocystis jirovecii* pneumonia (PJP) (previously called *Pneumocystis carinii* pneumonia), tuberculosis (TB), candidiasis, *Cytomegalovirus* (CMV) disease, *Mycobacterium avium* complex (MAC) disease, chronic parasitic diarrhea, toxoplasmosis, and cryptococcosis.[2,3,7-14] Findings of some studies suggest differences in the magnitude and types of HIV-related OIs seen in LMICs,[7-11] and high-income countries (HICs).[12-14]

Before the introduction of antiretroviral therapy (ART), progression to AIDS and premature death was the reality for HIV-infected individuals in both HICs and LMICs. During that period, AIDS-related deaths where overwhelmingly attributed to OIs. In the era of highly active ART (HAART), a significant decline in the magnitude of OIs as well as overall morbidity and mortality in HIV-infected populations have been demonstrated in various populations.[15-18] Nevertheless, available reports suggest that OIs remain an important cause of morbidity and mortality in PLHIV in the era of HAART in several populations.[19-21] Considering that access to HAART and optimization of antiretroviral treatment options have not been uniform among HIV-infected populations across various socioeconomic divides,[19] the positive impact of HAART in reducing the magnitude of HIV-related OIs may therefore have regional dimensions.

This review has three major objectives: First, to compare the overall incidence (or prevalence) of HIV-related OIs between HICs and LMICs in predominantly pre-HAART populations. Second, to highlight any disparities between LMICs and HICs in the frequency of individual OIs documented in available studies. Finally, to compare the impact of HAART on the magnitude of HIV-related OIs between the two socioeconomic settings.

Materials and Methods

Search strategy

Online databases and search engines including PubMed, Google, Google Scholar, and African Journal on-line were searched for articles published on HIV-related OIs from the onset of the epidemic up to December 31, 2013. Key words and expressions used for the search included "HIV-related opportunistic infections," "HIV-related opportunistic diseases," "HIV-associated opportunistic infections," "HIV-associated opportunistic diseases," "AIDS-related opportunistic infections," "AIDS-related opportunistic diseases," "AIDS-associated opportunistic infections," "AIDS-associated opportunistic diseases," and "AIDS-defining illness". The search was limited to articles published in English. A total of 14,431 articles were initially identified. After elimination of duplicates and studies that were not relevant to OIs in the setting of HIV/AIDS, 2,183 studies remained. Available full articles or abstracts of these studies were scrutinized to identify those that met the inclusion criteria. References of relevant articles were also checked. After exclusion of articles that did not meet the inclusion criteria, 77 articles that met the inclusion criteria were reviewed. The selection flowchart for papers reviewed is shown in Figure 1.

Selection criteria

Studies that met the following criteria were included: (a) Study was conducted in a setting (s) easily identifiable as HIC, LMIC as defined by the World Bank in 2013,[22] (b) age of the participants was ≥12 years, (c) the HAART status of the study population was stated, (d) the study investigated various types of OIs in an HIV-infected population rather than a single OI.

Ethical considerations

The author did not receive any funding for this review, and there are no personal, political, or academic competing interests. Accurate data extraction was ensured as much as possible. Extracted duplicate publications were deleted, and any other discrepancies were resolved before articles were

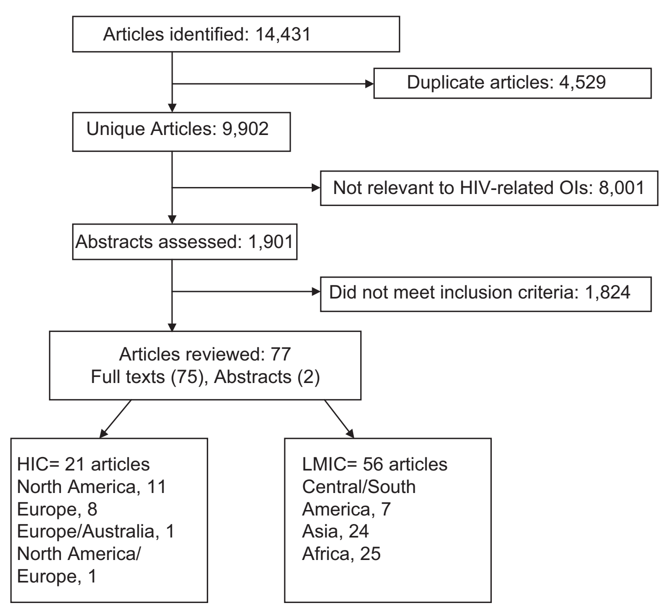

Figure 1: Flow chart for selection of papers. HIC: High income country, LMIC: Low/middle-income country, OI: Opportunistic infection

included in the review. Articles that met the eligibility criteria were included in the review irrespective of whether their findings were positive or negative.

Terminologies

ART-naive population referred to those who did not receive any form of ART.

HAART population referred to individuals who received ART (of any duration) made up of three drugs from at least two antiretroviral classes irrespective of whether a protease inhibitor (PI) was used.

Bearing in mind that classification of HAART status as previously described by Detels *et al*.,[23] using the 1996 cut-off calendar period (before 1996- pre-HAART; 1996 and beyond- post-HAART) may not be generalizable to several settings in LMICs that were yet to have established access to HAART around 1996, when the terms pre-HAART and post-HAART were used for specific studies, the calender periods being referred to were highlighted.

Chronic diarrhea as used in this review referred to cases mainly caused by cryptosporidium and/or *Isospora belli*.

HIV-related (or HIV-associated) OI included both AIDS-defining and non-AIDS defining OIs. This general term was adopted to harmonize the differences among the studies. Some studies investigated for only AIDS-defining OIs while others included non-AIDS defining OIs. Among the studies that investigated for only AIDS-defining OIs, various criteria were used such as CDC, 1987;[24] WHO, 1990;[25] CDC, 1993;[26] and WHO, 2005.[27]

Results

Seventy-seven publications met the study's inclusion criteria. Twenty one studies were conducted in HICs while the remaining 56 were carried out in LMICs. In HICs, there were 14 prospective cohort studies, 5 retrospective cohort studies, 1 randomized control trial and 1 bidirectional study with prospective, and retrospective arms. In LMICs, 20 studies had a prospective cohort design, 14 were retrospective analysis, 20 were cross-sectional studies, 1 was bidirectional (both prospective and retrospective arms), and 1 had both retrospective and cross-sectional designs. The findings of these studies are highlighted below and summarized in Tables 1-3.

Overall magnitude of opportunistic infections

Tables 1 and 2 summarize the studies that reported the overall incidence or prevalence (respectively) of OIs among predominantly pre-HAART populations in both HIC and LMIC. The overall incidence of HIV-related OIs in various studies in the HIC of the United States of America, Western Europe, and Australia ranged from 4.5 to 50.0 per 100 person-years (PY) of follow-up.[15-17,20,28-35] Fewer studies reported the overall prevalence of HIV-related OIs in HICs and found rates of 27 [1,493/5,451]–57 [228/402]%.[12,13,41] The majority of studies in HICs reported only the first episodes of HIV-related OIs[12,15-17,30-32,34,35] while others included any incident OI that occurred during the study.[13,28,33]

In LMICs of Asia, South/Central America, and sub-Saharan Africa, the overall incidence of HIV-related OIs was 12.2–93.9 per 100 PY.[18,36-40] Several studies reported the overall prevalence of OIs in LMICs and the range was 32.0 [66/207]–77.7 [136/175]%.[7-11,42-49] As was the case in HICs, most of these studies reported only the first HIV-related OI events[7,9,10,18,36,38,39,41,44] while others included any incident OI that occurred during the study.[8,40,42,47]

Magnitude of individual opportunistic infections

The frequency or incidence of individual OIs reported in various HICs and LMICs are presented below on the regional basis. In each region, the frequency of individual OIs as a proportion of total OIs documented is presented first followed by reports of incidence rates for individual OIs where available.

North America

In a survey of 6682 HIV-infected patients spanning 1990–1994 in the United States, 1883 died from OIs. The OIs that were most frequently experienced were PJP 45%, MAC disease 25%, CMV disease 23%, and esophageal/pulmonary candidiasis 22%.[2] The predominance of candidiasis (0.5–13.0 per 100 PY), PJP (0.4–9.0 per 100 PY), MAC (0.3–7.0 per 100 PY), CMV (0.2–7.0 per 100 PY), and Kaposi's sarcoma (KS) (2.5 per 100 PY) among OIs that occurred in predominantly pre-HAART US cohorts was also highlighted by other studies that documented their incidence rates.[15,28,29,51]

Western Europe and Australia

The frequency of individual OIs reported in various studies in Europe was fairly reflective of the predominant pattern in HIC. The frequently reported OIs were: CMV (9–37%),[34,52,53] PJP (10–29%),[34,52,53] toxoplasmosis (2.1–37%),[34,52,53] candidiasis (8–23%),[34,52,53] KS (7–28%),[34,52,53] and MAC (8–17%).[34,52,53] TB (7–11%),[52,53] and cryptococcosis (7%)[52] were less frequently experienced.

The incidence of individual OIs in studies conducted in Europe and Australia were as follows: Toxoplasmosis (1.5–12.6 per 100 PY),[16,33,54] PJP (1.5–11.4 per 100 PY),[16,17,33,35,54] candidiasis (1.7–11.0 per 100 PY),[16,17,33,35,54] MAC (0.37–9.5 per 100 PY),[16,17,33,35,54] CMV (0.59–6.8 per 100 PY),[16,17,33,35,54] TB (0.64–3.6 per 100 PY),[16,33,35,54] and chronic diarrhea (0.6 per 100 PY).[33]

Central and South America

In Central and South America, the frequently reported OIs included KS (5–47%),[46,55] candidiasis (12–44%),[11,46,56,57] TB (9–32%),[11,46,55-57] chronic diarrhea (3–33%),[11,46,56,57]

Table 1: Studies that reported overall incidence of opportunistic infections in predominantly pre-highly active antiretroviral therapy populations in high and low/middle-income countries

Study, year of publication	Setting and design	Remarks	Study period	OI incidence (/100 PY)
High-income countries				
1996[28]	USA, RCT	*n*: 1530 Age: 31 (12-66) years *** Male/female: 9:1 CD4 inclusion criteria: ≤300 cells/µl Repeat OI events included OI criteria: CDC, 1993 Randomized for monotherapy with zidovudine or didanosine	October 1989 to April, 1992	23.6 per 100 PY
1998[20]	USA, prospective cohort	*n*: 1255 Age: 80% were 30-49 years Male/female: 4:1 CD4 inclusion criteria: <100 cells/µl OI criteria: not clearly stated Likely all incident OIs 75% ART-naive or monotherapy in 1994; 94% on cART by June 1997	January 1994 to June 1997	50 per 100 PY
2000[29]	USA, prospective cohort	*n*: 8074-11,589 Age ≥13 years Male/female: 4:1 CD4 inclusion criteria: None OI criteria: Not clearly stated Likely all incident OIs 58% on HAART by 1998	1996-1999	16 per 100 PY
2004[30]	USA, prospective cohort	*n*: 2255 Only women without previous AIDS CD4 inclusion criteria: None Only first OI event after enrolment OI criteria: CDC, 1993 Predominantly ART-naive and non-HAART populations	December 1989 to June 2002	4.52 per 100 PY (before February 1994)
2009[31]	USA, prospective cohort	*n*: 614 MSM CD4 inclusion criteria: None Only first OI event after enrolment OI criteria: CDC, 1993 99% on non-HAART regimen before 1996 (defined as pre-HAART era)	1984-2007	7.55 per 100 PY (before 1996)
2010[15]	USA, prospective cohort	*n*: 8070 (4231 beeween 1994-1997) Age: 38 years* Male/female: 4:1 CD4 inclusion criteria: None Only first OI event after enrolment OI criteria: CDC, 1993 1994-1997: 25% ART-naive, 46% non-cART, 29% cART	January 1994 to December 2007	8.9 per 100 PY† (1994-1997)
1998[32]	Canada, retrospective cohort	*n*: 2533 Age: 38 (34-44) years** Male/female: 7.6:1 CD4 inclusion criteria: None Only first OI event after enrolment OI criteria: CDC, 1993 Newer and cART commenced in 1995	January 1994 to December 1996	8.0 per 100 PY (1994)
1999[17]	England, prospective cohort	*n*: 1806 (286 before 1992) Age: 32.3 (27.8-38.3) years** CD4 inclusion criteria: None Median CD4: 321 (120-520) cells/µl Only first OI event after enrolment OI criteria: CDC, 1993 Monotherapy was the only form of treatment before 1992	1987-1998	27.4 per 100 PY (before 1992)

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Table 1: Contd...				
Study, year of publication	**Setting and design**	**Remarks**	**Study period**	**OI incidence (/100 PY)**
2003[33]	Spain, prospective cohort	*n*: 2011 (1115 in January 1989) Age: 31 (17-78) years*** Male/female: 3:1 CD4 inclusion criteria: ≤500 cells/µl OI criteria: Not clearly stated Any incident OI during follow-up 15% monotherapy, 50% dual therapy and 35% HAART in 1997	January 1989 to December 1997	36.4 per 100 PY (1989)
1999[16]	Switzerland, prospective cohort	*n*: 2410 Age: ≥16 years Male/female: 2.8:1 CD4 inclusion criteria: None Only first OI after enrolment OI criteria: CDC, 1993 HAART introduced September 1995	September 1995 to December 1997	15.1 per 100 PY (in the 6 months before September 1995)
2000[34]	51 Centres across Europe (including Israel)	*n*: 7300 (3047 by January 1995) Age: >16 years CD4 inclusion criteria: <500 cells/µl Median CD4: 166 (44-300) cells/µl OI criteria: CDC, 1993 Only first OI after enrolment HAART for the majority in January 1999	May 1994 to Spring 1999	30.7 per 100 PY (1994)
2002[35]	10 European countries and Australia, retrospective cohort	*n*: 6041 Patients wth known dates of seroconversion spanning 1979-2000 Age: 28 (15-86) years*** Male/female: 4:1 CD4 inclusion criteria: None Only first OI event after enrolment OI criteria: European AIDS case definition, 1993 Dominanted by ART naive and non-HAART populations	Data pooled in 2001	8.02 per 100 PY† (1994-1996)
Low/middle income countries				
2009[36]	India, prospective cohort	*n*: 457 Age: 34 (male); 28 (female) years* Male/female: 6:1 CD4 inclusion criteria: None Median CD4 (cells/µl) 197 (male), 413 (female) Any incident OI during follow-up OI criteria: WHO, 2005 90% were ART-naive	September 2002 to November 2004	35.7 per 100 PY
2011[18]	Thailand, prospective cohort	*n*: 639 Age: 32 (29-37) years** Male/female: 1:1.4 CD4 inclusion criteria: None CD4: 152 (25-348) cells/µl Only first OI event after enrolment OI criteria: Not clearly stated 23% had history of ART use as mono or dual therapy	July 2000 to October 2004	19.1 per 100 PY
2002[37]	Brazil, retrospective arm of a birectional cohort	*n*: 64 Age: 39.9 (9.3 years)**** Male/female: 2.6:1 CD4 inclusion criteria: At least one CD4 at least ≤100 cells/µl Only first OI event after enrolment OI criteria: CDC, 1993 All patients had history of ART as mono (67%) or dual (33%) therapy	September 1997 to December 1999	51 per 100 PY

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Table 1: Contd...

Study, year of publication	Setting and design	Remarks	Study period	OI incidence (/100 PY)
1999[38]	Brazil, prospective cohort	*n*: 145 Age: 35 (18-67) years***** Male/female: 2.6:1 CD4 inclusion criteria: None CD4: 492 (332) cells/µl OI criteria: CDC, 1987 Only first OI event after enrolment ART with multiple drugs commenced November, 1996	1986-1997	12.2 per 100 PY
2007[39]	Cote d'Ivoire, prospective cohort	*n*: 608 Age: 31 (26-7) years** Male/female: 1:2.3 No CD4 inclusion criteria CD4: 290 (161-477) cells/µl OI criteria: Not clearly stated Reported OI incidence in sequence OI events stated for ART-naive only	1996-2003	40.6 per 100 PY (1st events) 68.4 per 100 PY (second events) 93.9 per 100 PY (3rd events)
2005[40]	South Africa, prospective cohort	*n*: 1215 Age: 31.3 (8.9) years**** Male/female: 1:1.1 No CD4 inclusion criteria Any incident OI after enrolment OI defined by WHO, 1990 ART naive	1992-2000	21.3 per 100 PY

†15Values were converted from incidence rates per 1000 person years of follow-up to 100 person years of follow-up, Age: *Median, **Median (IQR), ***Median (range), ****Mean (SD), *****Mean (range), ******Mean. *n*: Sample size, AIDS: Acquired immunodeficiency syndrome, ART: Antiretroviral therapy, c-ART: Combination antiretroviral therapy, CDC: Center for disease control and prevention, HAART: Highly active antiretroviral therapy, MSM: Men who sleep with men, OIs: Opportunistic infections, WHO: World Health Organization, SD: Standard deviation, IQR: Interquartile range, RCT: Randomized controlled trial, PY: Person years

PJP (13–29%),[11,46,55-57] toxoplasmosis (4–18%),[11,55-57] and cryptococcosis (5–14%).[11,55-57] CMV (2–5%),[11,46,55-57] and MAC (1%)[11,56,57] were infrequent conditions. None of the available studies documented incidence rates for individual OIs.

Asia

The OIs that were more frequently documented in Asia included candidiasis (1–88%),[3,7,10,18,43-45,58-67] TB (11.3–71%),[3,7,8,10,42,44,45,58,59,62-66,68-71] chronic diarrhea (0.3–47%),[3,7,8,10,43-45,58-67,69] CMV (1–45%),[3,7,10,18,43-45,58-64,67,71] and cryptococcosis (2–38%).[3,7,8,10,18,42,44,58,59,62-64,66,67] Other conditions were less frequently reported including PJP (1–23%),[3,8,10,42,58,59,62,63,67,68] toxoplasmosis (1–11%),[3,8,10,18,58,64,66,67] and MAC (2–3%).[64,65] KS was not documented in the available studies.

The incidence of individual HIV-related OIs was documented by Ghate *et al.*[36] in 457 cohorts in India. TB was the most common condition with an incidence of 15.4 per 100 PY, followed by candidiasis (11.3 per 100 PY). Cryptococcal meningitis was relatively less common at 1.7 per 100 PY while the incidence of each of PJP, CMV, and toxoplasmosis were <1.7 per 100 PY.

Sub-Saharan Africa

In sub-Saharan Africa, the frequency of individual OIs were as follows: TB (13–64%),[6,9,22,47-49,72-84] candidiasis (11–42%),[9,48,49,75-79,81,83] cryptococcosis (1–39%),[9,22,47,49,74-79,81,83-85] chronic diarrhea (3–35%),[9,22,47,49,75-81] toxoplasmosis (2–24%),[9,47,78-81] KS (1–18%),[9,22,49,72,77,78,82] CMV (1–18%),[9,75,77,82] and PJP (0–5%).[22,47,76-81] MAC was not documented in any of the available studies in sub-Saharan Africa. None of the available studies documented incidence rates for individual OIs.

Impact of highly active antiretroviral therapy on the magnitude of human immunodeficiency virus-related opportunistic infections

Impact on incidence or prevalence of overall opportunistic infections

Since the introduction of HAART, a significant decline in AIDS progression and the burden of OIs have been observed globally.[8,9,16,83-86] Table 3 summarizes the findings of cohort studies that documented the effect of HAART on the overall incidence or prevalence of HIV-related OIs.

In the HICs of North America, Western Europe and Australia, the introduction of HAART led to the significant decline of about 42.8–96.6% in the overall incidence of HIV-related OIs.[14-17,20,30-35] In the LMIC of South/Central America, Asia and sub-Saharan Africa, the decline in the overall incidence of OIs was about 30.0–79.0%.[11,18,36,37,39] In three studies that reported the effect of HAART on the overall prevalence of OIs in LMIC, the percentage reduction was about 38.3–47.0%.[8,9,46,50] As shown in Table 3, the HAART-induced decline in the overall incidence of OIs in Ivorian cohorts was seen for the first, second and third events with the percentage decline in OI events higher for subsequent events.[39] De Beaudrap *et al.*[9] in Senegal found

Table 2: Studies that reported overall prevalence of opportunistic infections in predominantly pre-highly active antiretroviral therapy populations in high and low/middle-income countries

Study, year of publication	Setting and design	Remarks	Study period	OI prevalence (%)
High-income countries				
1998[13]	USA, prospective cohort	*n*: 2081 Age: 35 (30-41) years** Male/female: 2:1 No CD4 inclusion criteria Median CD4: 264 cells/μl Any incident OI after enrolment Criteria: CDC, 1993 Pre-HAART era	January 1989 to June 1995	46
1997[12]	Germany, retrospective cohort	*n*: 1003 (402 in 1992) MSM Age: 38 years* CD4 inclusion criteria: <200 cells/μl Median CD4: 68 (63-73) cells/μl Only first OI event for each year OI criteria: CDC, 1993 27% ART-naive, 67% monotherapy in 1992	January 1992 to March 1997	56.7 (1992)
2007[41]	USA, prospective cohort	*n*: 5451 Newly diagnosed AIDS cases	2000	27.4
Low/middle income countries				
2002[7]	Thailand, retrospective cohort	*n*: 207 Age: 31 (28-57) years** Male/female: 3:1 CD4 inclusion criteria: None Only first OI events OI definition: Modified CDC, 1993 ART-naive	January 1997 to June 2000	32
2006[42]	India, prospective cohort	*n*: 438 Age: 77.9% were 20-40 years, 19.9% were >40 years Male/female: 4.2:1 CDC inclusion criteria: None Only first OI events OI definition: Not clearly stated ART-naive	November 1999 to December 2004	66.4
2011[10]	India, prospective cohort	*n*: 108 Age range: 21-50 years Male/female: 2:1 CD4 inclusion criteria: None Reported prevalence for OI events at baseline OI criteria: Not clearly stated ART-naive at baseline	Augeust 2006-2007	68.5
2011[43]	India, cross-sectional	*n*: 204 Age range: 9-66 years, 96.1%# were>20 years Male/female: 2:1 CD4 inclusion criteria: None OI criteria: CDC, 1993 Not clear if OI relapses were considered ART-naive	March 2006-2009	53.4
1999[44]	Thailand, prospective cohort	*n*: 2261 Age: 33.8 years****** Male/female: 5.7:1 CD4 inclusion criteria: None Mean CD4 Male: 979 cells/μl Female: 1158 cells/μl Only first OI events OI criteria: Modified CDC, 1993 ART-naive	November 1993 to June 1995	63.2

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Table 2: Contd...

Study, year of publication	Setting and design	Remarks	Study period	OI prevalence (%)
2010[45]	Lebanon, retrospective chart review	*n*: 89 Age: 35.4 (16-60) years***** Male/female: 3.5:1 CD4 inclusion criteria: None CD4: 131 (range 2-500) cells/µl Likely only first OIs events OI crieria: CDC, 1993 18% on ART including mono and dual therapy	1984 to January 2008	53.9
2006[8]	Taiwan, prospective cohort	*n*: 1044 (n: 175 in period 1) Age: 34 (15-75) years, period 1*** CD4 inclusion criteria: None CD4: 28 (1-762) cells/µl Any incident OIs events in period 1 OI criteria: CDC, 1993 59% were ART-naive at enrolment in period 1; HAART introduced in April, 1997	Entire study: June 1994-2005 Period 1: June 1994 to March 1997	77.7 (period 1)
2012[11]	Brazil, retroospective cross-sectional (pre-HAART arm)	*n*: 65 Age: 37.5 years****** Male/female: 3:1 CD4 inclusion criteria: None OI criteria: Not clearly stated Not clear if only first OI events Pre-HAART era	January 1991 to December 1995 (Pre-HAART)	70.8
2005[46]	Peru, retrospective cohort	*n*: 92 Male/female: 2:1 36% had CD4 <200 cells/µl OI criteria: CDC, 1993 Not clear if only first OI events ART-naive	January to December 2002	32.6
2012[47]	South Africa, retrospective cohort	*n*: 382 Age: 37 (31-44) years** Male/female: 1.1:1 CD4 inclusion criteria: <200 cells/µl CD4: 33 (12-78) cells/µl Only first OI events OI criteria: WHO, 2005 ART-naive	November 2006 to August 2007	32
2009[48]	Nigeria, cross-sectional	*n*: 606 Age range: 15-55 years Male/female: 3:2 CD4 inclusion criteria: None Only first OI events at enrolment OI criteria: Not clearly stated ART-naive	November 2005-2006	61.7
2011[49]	Nigeria, cross-sectional	*n*: 76 Age: 35 (8) years**** Male/female: 1:1.3 CD4 inclusion criteria: None Median CD4: 88 (12-522) cells/µl Only first OI events at enrolment OI criteria: CDC, 1993 ART-naive	October 2009 to November 2010	56.7

†15Values were converted from incidence rates per 1000 person years of follow-up to 100 person years of follow-up, Age: *Median, **Median (IQR), ***Median (range), ****Mean (SD), *****Mean (range), ******Mean, #Study was included in the review despite age range of 9-66 years because 96.1% of patients were >20 years and the remaining 3.9% of patients included those who were 12-20 years. *n*: Sample size, AIDS: Acquired immunodeficiency syndrome, ART: Antiretroviral therapy, CDC: Center for disease control and prevention, HAART: Highly active antiretroviral therapy, MSM: Men who sleep with men, OIs: Opportunistic infections, WHO: World Health Organization, SD: Standard deviation, IQR: Interquartile range, PY: Person years

that the overall incidence of OIs dropped from 20.5 per 100 PY in the 1st year of HAART to 4.3 per 100 PY in the 4th year post-HAART. However, unlike what was seen in several other populations that observed a progressive decline in OIs when patients on HAART were followed up on a long-term basis, the incidence of OIs in the Senegalese cohorts began to increase by 5% per month after the 4th year of HAART.

Table 3: Studies that documented the effect of highly active antiretroviral therapy on the overall incidence or prevalence of human immunodeficiency virus-related opportunistic infections in high and low/middle-income countries

Study, year of publication	Setting	Design	Overall OI incidence (per 100 PY) or prevalence (%)		Percentage of decline in OI incidence or prevalence
			ART-naive or pre-HAART	Post-HAART	
High-income countries					
1998[20]	USA	Prospective cohort (1994-1996) (*n*=1255)	50 per 100 PY (1994/1995)	28.6 per 100 PY (1996)	42.8
2010[15]	USA	Prospective cohort (1994-2007) (*n*=870)	8.9 per 100 PY† (1994-1997)	0.3 per 100 PY† (2003-2007)	96.6
2009[31]	USA	Prospective cohort (1984-2007) (*n*=614)	7.55 per 100 PY (before 1996)	2.08 per 100 PY (1996-2007)	72.5
2004[30]	USA and Puerto Rico	Prospective cohort (1989-1997) (*n*=2255)	4.52 per 100 PY (before February 1994)	1.22 per 100 PY (Auguest 1996-1997)	73.0
1998[32]	Canada	Prospective cohort (1994-1996) (*n*=2533)	8.0 per 100 PY (1994)	2.2 per 100 PY (1996)	72.5
2005[14]	13 cohorts in North America and Europe	Prospective cohort (1996-2000) (*n*=12,574)	12.93 per 100 PY† (within 3 months of HAART)	1.32 per 100 PY† (3 years post-HAART)	89.8
2002[35]	10 European countries and Australia	Prospective cohort (1994-2000) (*n*=6941)	8.02 per 100 PY† (1994-1996)	2.53 per 100 PY† (1997-2000)	68.5
1999[17]	England	Prospective cohort (1987-1998) (*n*=1806)	27.4 per 100 PY (on or before 1992)	6.9 per 100 PY (1997)	74.8
2000[34]	51 Centres in Europe (including Israel)	Prospective cohort (1994-1999) (*n*=7300)	30.7 per 100 PY (1994)	2.5 per 100 PY (1998)	91.9
1999[16]	Switzerland	Prospective cohort (1995-1997) (*n*=2410)	15.1 per 100 PY (6 months before HAART)	2.2 per 100 PY (9-15 months post-HAART)	85.4
2003[33]	Spain	Prospective cohort (1989-1997) (*n*=1115)	36.4 per 100 PY (1989-1991)	14.6 per 100 PY (1997)	59.9
1997[12]	Germany	Prospective cohort (1992-1997) (*n*=1003)	56.7% (1992)	20.7% (1996)	64.7
Low/middle-income countries					
2011[18]	Thailand	Prospective cohort (2000-2004) (*n*=704)	19.1 per 100 PY (pre-HAART)	8.2 per 100 PY (post-HAART)	57.1
2009[36]	India	Prospective cohort (2002-2004) (*n*=457)	37.3 per 100 PY	23.9 per 100 PY	35.9
2002[37]	Brazil	Bidirectional cohort (1997-1999) (*n*=79)	51.0 per 100 PY (pre-HAART)	29.0 per 100 PY (post-HAART)	43.1
2010[9]	Senegal	Prospective cohort (1998-2008) (*n*=404)	20.5 per 100 PY (1st year post-HAART)	4.3 per 100 PY (4th year post-HAART)	79.0
2007[39]	Cote d'Ivoire	Prospective cohort (1996-2003) (*n*=608)	40.6 per 100 PY (1st OI event)	28.4 per 100 PY (1st OI event)	30.0
			68.4 per 100 PY (2nd OI event)	39.4 per 100 PY (2nd OI event)	42.4
			93.9 per 100 PY (3rd OI event)	37.6 per 100 PY (3rd OI event)	60.0
2012[11]	Brazil	Retrospective cross-sectional	70.8% (1991-1995) (*n*=65)	37.5% (2002-2009) (*n*=237)	47.0
2005[46] 2007[50]	Peru	Retrospective cohort (1994-2003)	32.6% (*n*=92)	20.0% (*n*=564)	38.7
2006[8]	Taiwan	Prospective cohort (*n*=1044)	77.1% (1994-1997)	47.6% (2000-2004)	38.3

†15Values were converted from Incidence rates per 1000 person years of follow-up to 100 person years of follow-up, *n*: Sample size, HAART: Highly active antiretroviral therapy, OI: Opportunistic infection, PY: Per year

Magnitude of individual opportunistic infections in the post-highly active antiretroviral therapy era

Generally, the magnitude (incidence or prevalence) of individual OIs among HIV cohorts post-HAART was reported by few studies. In HICs, the cohort studies that reported incidence of individual OIs post-HAART found the following rates per 100 PY: Candidiasis 1.0–5.7,[16,17,33,35] MAC 0.6–2.7,[16,17,33,35] CMV 0.6–5.1,[16,17,33,35] PJP 0.2–4.4,[16,17,33,35] KS 0–2.3,[16,17,33,35] TB 0.2–2.6,[16,33,35] toxoplasmosis 0.2–1.8,[16,33,35] and cryptococcosis 0.6.[33] The frequency of individual OIs in HICs reported in two cohort studies were: CMV 1.8–7.7%,[15,34] PJP 3.9–11%,[15,34] MAC 2.5–6.2%,[15,34] candidiasis 5.4–19%,[15,34] KS 1.2–8%,[15,34] TB 0.8–1.9%,[15,34] toxoplasmosis 0.5–1.3%,[15] and chronic diarrhea 0.8–2%.[15]

In four cohort studies, the following frequency of individual OIs among HIV-infected patients post-HAART in LMICs was found: TB 13.0–38.2%,[8,9,11,18] candidiasis 11.0–23.1%,[8,9,18] cryptoccosis 0–20.6%,[8,9,11,18] CMV 0–23.1%,[8,9,11,18] PJP 0–29.5%,[8,9,11,18] KS 0–5.2%,[8,9] MAC 15.4–18.2%,[8] and toxoplasmosis 0–8.8%.[8,9,11,18]

Retention in human immunodeficiency virus care

Retention in HIV care is required for optimal clinical outcomes including reducing the magnitude of OIs. Available literature shows that definitions of retention in HIV care are rather heterogenous. According to the WHO, “Retention in HIV care” can be defined from the moment of initial engagement in care, when a person with HIV is linked successfully to services, to assessment for eligibility, initiation on ART, and retention in lifelong ART care.[87] However, in other studies and reports, it sometimes includes the period from diagnosis to successful linkage to care.[87]

Some studies in Western countries have assessed retention in care from such comprehensive perspectives. In a meta-analysis of 28 US studies with a total of 75, 655 HIV-diagnosed persons, it was reported that 59% of them, regardless of the length of time since diagnosis, were retained in care.[88] Retention in care was defined regarding multiple HIV medical care visits averaged across the assessment intervals. The estimate increased to 62% after omitting the two studies that had long assessment intervals of 3 and 5 years. The percentage of HIV-diagnosed persons retained in care was higher in studies conducted before 2003 (62%) than in studies conducted in 2003 or more recently (42%).[88]

In the United Kingdom, the 12-month retention rate of all 72,840 adults seen for HIV care in 2011 was 95%.[89]

In HIV treatment programs in resource-limited settings, retention in care has been defined as “patients known to be alive and on ART at the end of a follow-up period either at the same facility or formally transferred out to another ART unit and thus assumed to be on therapy.”[90,91] A large systematic review in 2007 that surveyed 32 publications on 33 cohorts comprising 74,289 patients in 13 countries reported a plausible mid-point estimate of retention 2 years after ART initiation of 50% among HIV-infected patients on ART in Africa.[90] The analysis was updated in 2010 using an additional 39 cohorts of 226, 307, and it was found that the 24-month retention rate was 70.0%.[92]

Considering that most reports of retention in HIV care are based of clinic perspectives, it is likely that patients who are lost to follow-up have been assumed to have disengaged from care. However, in the setting of rapid ART scale-up and decentralization of care, this assumption may not always be true.[93] Some studies in Africa have shown that 50–55% of HIV-infected patients on ART who were lost to follow-up and found to be alive following contact tracing were still in care elsewhere.[94,95]

So far, there is a paucity of literature on long-term retention on ART (after 24 months), making this an important area for further study, especially in the light of recent changes in the WHO treatment guidelines, recommending treatment initiation at ≤500 cells/μl.

Discussion

In this review, the magnitude of HIV-related OIs in predominantly pre-HAART populations in both HIC and LMIC were described, and the percentage decline in the magnitude of OIs following the introduction of HAART was further highlighted in the two socioeconomic settings. The incidence or prevalence of overall HIV-related OIs was generally high in predominantly pre-HAART populations in both settings, but LMIC appeared to have higher OI incidence and prevalence. There were also disparities in the types of OIs predominant in each socioeconomic setting. While PJP, candidiasis, CMV disease, MAC disease, KS, and occasionally toxoplasmosis were predominant in HICs; TB, candidiasis, chronic diarrhea, and cryptococcosis were consistently more frequent in LMICs. Substantial reductions in the overall incidence or prevalence of OIs were documented following the introduction of HAART both in HICs and LMICs, but the percentage decline appeared more impressive in HICs.

There are a number of reasons for the apparent disparities in HIV-related OIs between HICs and LMICs. First, the methodological differences in the various studies reviewed could account for this. While the majority of the findings of HICs were based on the large prospective cohort studies, studies in LMICs mainly involved prospective or retrospective cohorts, or some cross-sectional studies with relatively smaller sample sizes. There were also some subtle differences in the definition of diseases selected for inclusion as OI in the various studies. In some studies, there were immunological criteria for inclusion, and this would strongly influence the spectrum of OIs since certain OIs are more commonly encountered with more severe degrees of immunosuppression. There is overwhelming evidence that low baseline CD4+ cell count[16,36,54,64,96-99] and low CD4+ cell count during ART[16,29,100] are strong risk factors for OIs both in HICs and LMICs.

Beyond issues that bother on methodology, it has been shown that geographical differences may have a role to play in the reported incidence of HIV-related OIs.[54] This may explain why PJP and KS appeared relatively more frequent in Central/South America than the other LMICs of Asia and sub-Saharan Africa. Nevertheless, the apparent rarity of MAC, CMV, and sometimes PJP in LMICs possibly raises concern on the role of local diagnostic capacity in the magnitude of reported OIs. The fact that a good number of centers in LMICs, especially sub-Saharan Africa do not have sufficient diagnostic facilities for these three conditions should be borne in mind before drawing strong inferences on the burden of these OIs in LMICs.

The role of racial factors in predicting the incidence or types of OIs in HIV-infected populations have also been investigated. In an evaluation of the profile of OIs in HIV-infected persons living in Australia,[101] PJP was clearly, the most commonly diagnosed condition in people of all country/region of birth except for individuals born in sub-Saharan Africa. Those born in sub-Saharan Africa had an increased risk of TB and cryptococcosis but a decreased risk of PJP and esophageal candidiasis compared to individuals born in Australia even after adjusting for length of stay in Australia. TB risk was also higher among those born in Asia-Pacific and other low-income countries, but the risk of various types of OIs was similar for HIV-infected patients born in Australia and other industrialized countries. According to Del Amo *et al.,*[102] TB accounted for 27% of the initial episodes of AIDS-related OIs in Africans but 5% in non-Africans while PJP was the initial AIDS-related condition in 34% of non-Africans but 17% for Africans. In Netherlands, it was reported that compared to patients from Western Europe, Australia, and New Zealand, patients of sub-Saharan African origin had a significantly lower risk for PJP both at the time of HIV diagnosis and during follow-up while in care after adjusting for confounders.[98] The authors suggested that differences in genetic susceptibility may partially explain the lower PJP incidence in the African patients.

The introduction of HAART was associated with substantial reduction in the incidence of OIs both in HICs and LMICs. To some extent, regarding percentage decline in the burden of OIs following the introduction of HAART, the findings of this review suggest a somewhat more impressive impact in HICs, which has apparently enjoyed earlier, wider, and more durable access to HAART. Beyond the earlier introduction of HAART in HICs compared to most LMICs, antiretroviral drug options are better in HICs. The wide availability of PIs in HICs possibly lays credence to this. In 12,574 HIV cohorts from 13 HICs in Europe and North America, 85.6% of patients initiating HAART between mid-1990s and 2000 were commenced on a PI-based regimen.[14] At the end of 2010 <5% of HIV-infected individuals in LMICs (excluding South and Central America) were receiving PI-containing regimens mainly as second-line ART.[19] However, the comparison of the impact of HAART on the magnitude of OIs between HICs and LMICs was further complicated by the observation that studies accessing the impact of HAART on OIs in LMICs lagged behind those of HICs by 5 years or more. In the event of possible differences in HAART-induced decline in OI incidence between people of diverse socioeconomic settings, it becomes necessary to unravel any other key factor(s) that may affect the risk of OIs in patients receiving HAART.

HIV-infected patients on HAART who have poorer socioeconomic living conditions have been found to have higher risk of OIs. Iroezindu *et al.*[96] found that poor household income was an independent predictor of OIs among Nigerian patients on HAART. Badri *et al.*[103] also reported that low socioeconomic status was significantly associated with incident TB during HAART in South Africa. While poor living conditions may not be a critical problem in HICs, failure to determine the effect of poverty on the development of OIs in the era of HAART in LMICs would be a fundamental oversight.

The findings of this review have important regional and global public health implications in the management of HIV/AIDS. First, the efficacy of HAART in reducing OI morbidity and its attendant mortality in PLHIV has been shown beyond reasonable doubt irrespective of socioeconomic differences. However, despite emerging evidence of the significant burden of noninfective morbidity in PLHIV in a number of studies.[104,105] OIs continue to be a problem even in the era of HAART as the burden of disease is still considerable in several populations. Since the somewhat more impressive percentage decline in OI burden reported in HICs compared to LMICs may not be unconnected with the earlier, wider, and more durable access to HAART, it re-emphasizes the need for intensification of the scaling up of ART in resource-limited settings.

The findings of this study should be interpreted in the light of its strengths and limitations. One of the strengths of this review is that the period considered spanned the entire three decades of the HIV/AIDS epidemic. Moreover, the studies included in this review involved patients in all the continents of the world. In addition, the majority of the studies reviewed reported incidence rates which adjusted for population size and period under exposure thereby allowing for some reasonable comparisons between studies with different sample sizes. A major limitation of this review regarding the overall incidence or prevalence of OIs is the differences in the definition of diseases selected for inclusion as OI in the various studies. While some studies investigated only AIDS-defining conditions, others included non-AIDS-defining OIs depending on the peculiarities of their geographical region. Second, there were relatively fewer studies from LMICs (especially sub-Saharan Africa) that performed active follow-up over long periods of time compared to HICs. In addition, in some countries or regions, only one or two studies published in English were found, and these studies may not necessarily be representative of the picture in the entire country or region. As a result of the unavailability of information regarding chemoprophylaxis for OIs in the majority of studies, this review was unable to assess the possible impact of OI chemoprophylaxis on the changes in OI incidence following the introduction of HAART. The lack of diagnostic capacity for certain OIs such as MAC and CMV diseases in several resource-limited settings also calls for caution while drawing conclusions on the actual incidence or prevalence of these OIs in LMICs.

Conclusion

This review found that the magnitude of HIV-related OIs was substantial in both HICs and LMICs before the introduction of HAART, but LMICs appeared to have higher OI incidence or prevalence. There were also disparities in the types of OIs frequently reported in each socioeconomic setting. It was further shown that the introduction of HAART led to substantial reductions in the overall incidence of OIs with somewhat more impressive impact in HICs. As our clinical concerns increasingly shift towards the growing burden of noninfective complications of HIV and its treatment, let us not erronously conclude that OIs have become a thing of the past. According to Brooks *et al.*,[106] "OIs are here to stay, and they will continue to demand our attention for the foreseeable future. They continue to occur among patients who are unaware of their HIV infection and among patients who, despite awareness of their HIV infection, remain unlinked to care, or if receiving care, are unable to assess optimal ART for several reasons." Incidentally, nearly all the factors that perpetuate OIs in the era of HAART as observed by Brooks *et al.*[106] are much more prevalent in LMICs. Should it then be appropriate to say that the achievements of the scaling up of ART in resource-limited settings may face a major threat in the face of these undermining factors? If this happens, any seeming disparity in the magnitude of HIV-associated OIs and the benefits of HAART between HICs and LMICs may inadvertently be widened in the era of HAART.

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Conflicts of interest

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