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An informetric investigation of the relatedness of opportunistic infections to HIV/AIDS

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Abstract

This work presents preliminary findings of a broader content analysis study of the AIDS literature as published and reflected in key bibliographic databases. Specifically, this study focuses on the relatedness of the AIDS-defining diseases in persons with documented HIV infection—otherwise known as Opportunistic Infections (OIs)—to HIV/AIDS by measuring their strengths of association. Ultimately, the project aims at assisting researchers and other stakeholders to identify new research areas and the linkages among these areas in HIV/AIDS research and assist policy makers to map the dynamics of HIV/AIDS research in order to do research planning and formulate appropriate policies. Among many other objectives, the current study sought to test the hypothesis that, through the analysis of published articles, one could show the disease–gene relationship. Documents related to OIs and HIV/AIDS were retrieved and downloaded from the MEDLINE database. The co-word analysis algorithm was used to calculate the strength S of association between the descriptors (i.e. the OIs and HIV/AIDS). The findings of this study correlate with the general observation by medical practitioners as regards the common OIs in AIDS patients. Those infections that are said to be the most common in HIV-infected persons exhibited stronger associations than the less common infections. The strength of association was highest with *pneumocystis carinii pneumonia* (PCP) while it was lowest with *Shigella*. Whereas the association between the diseases and HIV/AIDS has weakened over the last two decades, relatively, there has been continued growth of literature, both on HIV/AIDS and OIs. Finally, this study strongly demonstrates the use of informetrics techniques in assessing the relatedness of a disease to the pathogens that are associated with it.

Keywords: Information retrieval; Informetrics; Opportunistic infections; HIV infections; Acquired Immunodeficiency Syndrome; Information theory in research

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1. Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 40 million people are currently living with HIV/AIDS and that 92.5% of them are adults while the rest are children below the age of 15 years (UNAIDS, 2003). The report further shows that during the year 2003, approximately 5 million people were infected with Human Immunodeficiency Virus (HIV). Within the same period, Acquired Immunodeficiency Syndrome (AIDS) claimed 3 million lives.

Although it has elicited controversial observations concerning its cause, AIDS is generally believed to be the final stage of HIV infection. At its initial stage, HIV dramatically reduces the CD4+ T-cells, which are "central elements in the control of both humoral and cell mediated immune defenses" (Brookmeyer & Gail, 1994, p. 8). The third and last stage of the battle between HIV and the body's immune system, called clinical AIDS stage, begins with the decline of the total CD4+ T-cell count to approximately 200 per cubic millimeter of blood (World Bank, 1997).

This stage takes a few years after which the virus weakens the immune system to the point where the first "opportunistic infections" (OIs) manifest themselves. A further decline of these cells causes the body to easily succumb to the OIs and other illnesses, a situation that leads to death. Medical researchers have observed that HIV itself does not kill but, instead, it is the OIs that kill (Médecins Sans Frontières, 2003). Williams (1991, p. 34), for instance, observes that "there is very rarely an African who dies from AIDS or HIV diseases without a minimum of two opportunistic infections, established either on clinical grounds or confirmed at autopsy".

OIs are illnesses that make one sick due to the damaged or weakened immune system of the body caused by the HIV infection (Sowadsky, 1999; UNAIDS, 1998). They are caused by microbes such as viruses or bacteria that, under normal circumstances, do not make healthy people sick (National Institute of Allergy and Infectious Diseases (NIAID), 2003; West Penn Allegheny Health System for Patients and Public Health, 2003). Their association and/or relatedness to HIV/AIDS has been medically documented. In fact, it has been observed that some of these diseases are more common in persons with HIV/AIDS while others are less common (Cheesbrough, 2000; Médecins Sans Frontières, 2003; New Mexico AIDS Education & Training Center, 2003).

Whether this kind of association is reflected in the published literature on HIV/AIDS is the subject of this study. Secondly, this study examines the applicability of co-word analysis to evaluate the strength of association between OIs and HIV/AIDS. In other words, the study aims at assessing whether co-word analysis can be utilized to supplement other medical research methods, such as clinical surveys, in determining the relatedness of OIs and HIV/AIDS, on the one hand, and a disease and its associated pathogens, on the other.

2. An overview of co-word analysis

The origin and development of the concept of co-word analysis has been attributed to the increasing growth of information, which poses problems to scientists and policy makers. In the words of He (1999), "it is hard for scientists to detect the subject areas and the linkages among these areas in their research fields, and policy makers have difficulties in mapping the dynamics of science to do research planning". Secondly, the mapping of relationships among concepts, ideas, and problems in science called for the development of better quantitative analytic techniques, which currently include co-citation analysis, co-nomination analysis, co-classification, and co-word analysis (He, 1999; Kostoff, 2001).

Co-word analysis, sometimes referred to as co-occurrence analysis, has emerged as an essential bibliometric analytic tool in the assessment of the strength of association between two or more terms. It simply refers to the process of analysing the "co-occurrence of two or more words in one document or in different documents" (Diodato, 1994, 54). Krsul (2002) defines it as "a content analysis technique that is effective in

mapping the strength of association between keywords in textual data''. The technique focuses on analysis of term(s) within the text or keywords.

The origin of the co-word analysis method can be traced way back to the 1980's when French sociologists, from the school ''Ecole des Mines'', set out to examine the ''role of words and networks of words in literal texts describing evolving systems'' (Shyama & de Looze, 2001). In due course, they developed a methodology that was close to co-citation analysis, a method that was developed by the Institute for Scientific Information (ISI) and made possible through the creation of the Science Citation Index (SCI) by Eugene Garfield in 1964 in the USA. Shyama and de Looze (2001) observe that co-word analysis, as developed in France, was different from co-citation analysis in that it was applied to the *words* themselves in the literal text and not only to *authors*. Co-word analysis has since been developed by different authors to incorporate several approaches. It involves the preparation of an *Inclusion Index, Proximity Index* and the calculation of the *Equivalence Coefficient* (He, 1999). The application and importance of the method in mapping the content of research has been boosted with the development of co-word analysis tools such as Bibexcel and the analytic tool developed by Krsul, which is available at: http://www.acis.ufl.edu/~ivan/coword/ (Last accessed on Dec., 3rd 2003).

Several studies, with varying aims and objectives, have been conducted in a variety of disciplines using co-word analysis. The method has been used to identify knowledge communities in various sectors in public policy development (Neil, 2002) and to find out the most frequent topics in Library and Information Science (LIS) research (Uzun, 2002). It has also been used to trace intellectual structures of Information Retrieval (IR) (Ding, Chowdhury, & Foo, 2001) and as a means of increasing search variety for end users in the domain of IR (Ding & Chowdhury, 2000). He (2000) utilised the analytic technique to map the dynamics in artificial intelligence and concluded that it is possible to identify hot topics in a particular scientific field and map dynamics in the topics using co-word analysis. Similarly, Courtial and Law (1989) conducted a co-word study of artificial intelligence to determine the effectiveness of content analysis in the process of mapping research literature in software engineering. Whittaker (1989) applied co-word analysis on words in titles and keywords to explore the adequacy of the method in mapping literature on acidification research.

However, one of the very important developments that led to the current study can be found in a study conducted by Takahata, Asano, Kouchi, and Takagi (2003). These authors set out to test and further develop a hypothesis that could link a given disease to its genes by using published literature. In their study entitled ''Disease-Associated Genes Extraction from Literature Database'' the authors used the MEDLINE database to extract biomedical terms that they in turn used to determine the co-occurrence relations. Their preliminary findings suggest that ''automated creation of a hypothesis, which shows the disease-gene relations in a step-wise manner, could be feasible through analysis of published articles'' (2003:704).

3. Methods and materials

The diseases were purposefully selected from two sources, namely:

- A list of the Centers for Disease Control and Prevention's (CDC, 2002) AIDS-defining diseases in persons with documented HIV infection found in the Internet.
- Cheesbrough (2000, 257).

The selection of the OIs was done to strike a balance between the most common and less common infections. For purposes of this study, only those OIs that apply to both males and females were included in the sample of diseases. Documents related to these diseases were retrieved, downloaded and stored in electronic spreadsheets prepared with Microsoft Excel, version 2002.

3.1. Database

The source of the bibliographic data was the MEDLINE database. MEDLINE is an electronic database created by the National Library of Medicine and offers a wide range of information on such subjects as medicine, nursing, dentistry, veterinary medicine, the health care system, and pre-clinical sciences from over 4600 medical journals. MEDLINE uses the Medical Subject Headings to index documents. It includes citations from Index Medicus, International Nursing Index, Index to Dental Literature, PREMEDLINE, AIDSLINE, BIOETHICSLINE, and HealthSTAR.

3.2. Procedure

The preliminary exercise involved the preparation of a list of search terms. The online MeSH thesaurus that is linked to the EBSCO electronic publishing company's website was used to generate the list of the technical search terms. Table 1 provides a list of diseases with the corresponding positive MeSH terms/phrases used to search for relevant documents.

Basically, an online advanced Boolean search was conducted using the MeSH search terms in three stages:

- A general search was done for the documents related to HIV/AIDS. As the earliest document on HIV/AIDS was published in 1982, this year was chosen to be the starting point in subsequent searches involving the other OIs.
- A general search was done for the documents related to each of the OIs.
- The third set of data was collected through searching for documents related to the OIs within the AIDS subset of the MEDLINE database. In this way, all documents on OIs as they relate to HIV/AIDS were retrieved for analysis.

Table 1
List of positive MeSH search terms used to identify records on HIV/AIDS and opportunistic infections from the MEDLINE database

	Name of diseases	MeSH terms used in the search
1	HIV/AIDS	HIV; Acquired Immunodeficiency Syndrome
2	*Candida albicans*	*Candida albicans*
3	*Cryptococcus neoformans*	*Cryptococcus neoformans*
4	*Cryptosporidium parvum*	*Cryptosporidium parvum*
5	*Cytomegalovirus* and *Cytomegalovirus* infection	*Cytomegalovirus*; *Cytomegalovirus* infections
6	*Haemophilus influenzae*	*Haemophilus influenzae*
7	*Herpes simplex*	*Herpes simplex*
8	*Histoplasma capsulatum*	*Histoplasma*
9	*Isospora*	*Isospora*
10	*Mycobacterium avium-intracellulare* and *Mycobacterium avium-intracellulare infections*	*Mycobacterium avium-intracellulare* infection; *Mycobacterium avium* complex
11	*Mycobacterium tuberculosis*	*Mycobacterium tuberculosis*
12	*Pneumocystis carinii* and *Pneumocystis carinii* infection	*Pneumocystis carinii*; *Pneumocystis carinii* infections
13	*Salmonella*	*Salmonella*
14	*Shigella* and *Shigella* infection*	*Shigella*; Dysentery, Bacillary
15	*Staphylococcus aureus*	*Staphylococcus aureus*
16	*Streptococcus pneumoniae* and *Sreptococcus pneumoniae* infection	*Streptococcus pneumoniae*; Pneumococcal infections
17	*Toxoplasma* and Toxoplasmosis	*Toxoplasma*; Toxoplasmosis
18	*Varicella zoster*	*Herpesvirus* 3, Human

* A search was conducted on the *Shigella* infections and their causal bacteria.

The search was limited to the "word in subject heading" field, simply referred to as MW. We preferred the use of the MW search strategy to other similar techniques because it allows users to search using the indexed word, both as *major* and *minor* heading words, within the subject headings. Comparatively, the "exact subject heading (MH) mode employs the use of a phrase to search the *exact* MeSH subject heading within both the major and minor headings, while the "word in major subject heading" (MJ) uses a "*major*" indexed word to search for words in the MESH subject headings. On its part, "exact major subject heading" (MM) employs the indexed phrase to search for the *exact* MeSH heading as only a *major* concept of the article.

Having extracted and recorded the data on the electronic spreadsheets, we analyzed the data using MS Excel 2002 software. Two co-occurrence matrices were constructed. The first matrix consisted of the frequency of co-occurrence of HIV/AIDS with each of the 17 OIs covered in this study. The purpose was to determine the relatedness of OIs to HIV/AIDS. The second matrix aimed at assessing the relatedness of one opportunistic disease to the other.

In order to determine how closely linked an OI is to HIV/AIDS, the infection's strength of association was calculated. An OI whose strength of association was closer to 1 was said to be more closely associated with HIV/AIDS, while an OI whose strength of association was closer to 0 (zero) was said to be rarely associated with the epidemic. The underlying principle is stipulated in Krsul (2002) who observes that "keywords that often appear together will have strengths closer to 1, and keywords that appear together infrequently will have strengths closer to 0".

The co-word analysis algorithm was used to calculate the strength S of association between the descriptors (i.e. the diseases and HIV/AIDS). The formula was applied to the two co-occurrence matrices to produce two proximity indexes, which were used to calculate the association values. The strength S of association values, which were rounded up to six decimal places, were measured using the following formula, as set out in Krsul (2002) and He (1999).

$$S = C_{ij}^2 / C_i \cdot C_j$$

where C_{ij} is the number of documents in which the keyword pair (M_i and M_j) appears, C_i is the number of documents in which keyword M_i appears C_j is the number of documents in which keyword M_j appears.

Data analysis and presentation was done using tables and graphs, which were collected and interpreted accordingly. Whereas data were tabulated to depict the overall distribution of publications by year of publication, the graphical representation of the same data gave a pictorial trend of research on, and the association between HIV/AIDS and each OI, on the one hand, and among the OIs, on the other.

4. Results

This section presents the findings in five sub-headings, namely:

- HIV/AIDS and OIs research: year distribution of the records, 1982–2003.
- HIV/AIDS and Opportunistic Infections: Co-occurrence relations.
- HIV/AIDS and OIs: Strengths of Association.
- Opportunistic Infections: Co-occurrence relations.
- Opportunistic Infections: strengths of association.

4.1. HIV/AIDS and OIs research: year distribution of the records, 1982–2003

Table 2 presents the number of documents indexed in the MEDLINE under HIV/AIDS and various opportunistic infections from 1982 to 2003. The period of study has been divided into six three-year periods

Table 2
HIV/AIDS and OIs: Year distribution of records for the period 1982–2003

	1982–1984	1985–1987	1988–1990	1991–1993	1994–1996	1997–1999	2000–2003	Total
HIV/AIDS	1870	9275	22,317	27,008	27,296	28,295	32,159	148,220
Salmonella	3176	3105	3333	3576	3388	3368	4549	24,495
Staphylococcus aureus	2044	2318	2331	2665	2744	3171	4448	19,721
Cytomegalovirus	1301	1690	2048	2528	2905	2950	3345	16,767
Mycobacterium tuberculosis	618	610	826	1149	1707	2196	3395	10,501
Streptococcus pneumoniae	890	843	820	976	1463	1931	2867	9790
Candida albicans	704	874	970	1128	1284	1362	1928	8250
Toxoplasma	817	872	966	1242	1278	1242	1368	7785
Herpes simplex	1048	1105	977	957	886	935	1291	7199
Haemophilus influenzae	760	905	911	1089	914	949	1205	6733
Pneumocystis carinii	387	553	1001	1370	1224	946	709	6190
Shigella	671	610	610	632	577	539	568	4207
Varicella zoster	271	335	323	349	426	413	576	2693
Mycobacterium avium-intracellulare	0	0	290	464	733	564	446	2497
Cryptococcus neoformans	133	143	177	265	379	435	590	2122
Cryptosporidium parvum	0	0	0	110	246	376	485	1217
Histoplasma capsulatum	77	78	95	101	107	123	160	741
Isospora	25	32	20	44	53	49	43	266

for easy tabulation. The only exception is in the 2000–2003 time period, which comprises four years. This table serves two main purposes. Firstly, it is meant to assist in comparing research on HIV/AIDS and each OI through assessing the yearly distribution of relevant records as indexed in the database. Secondly, it is meant to provide the number of publications in which the diseases were independently analysed (i.e. C_i and C_j) for the subsequent analysis of the strength of association. That is, it is meant to obtain the frequency of occurrences of keywords M_i and M_j.

As Table 2 shows, HIV/AIDS leads the pack with 148,220 records. The second in the ranking is *Salmonella*, which has 24,495 records. These publications are roughly six times less those of HIV/AIDS. *Staphylococcus aureus* followed very closely with 19,721 publications followed by *Cytomegalovirus* and *Mycobacterium tuberculosis* with 16,767 and 10,501 records, respectively. The rest of the diseases, except for two, yielded less than 10,000 but more than 1000 records. These include *Streptococcus pneumoniae* (9790), *Candida albicans* (8250), *Toxoplasma* (7785), *Herpes simplex* (7199), *Haemophilus influenzae* (6733), and *Pneumocystis carinii* (6190). Others are *Shigella species* (4207), *Varicella zoster* (2693), *Mycobacterium avium-intracellulare* (2497), *Cryptococcus neoformans* (2122), and *Cryptosporidium parvum* (1217). *Histoplasma capsulatum* and *Isospora* produced 741 and 266 documents, respectively.

Throughout the entire period, HIV/AIDS maintained its lead in the number of records except for the period 1982–1984. The trend of publishing for each of the OIs and HIV/AIDS is shown in Fig. 1, which is a graphical representation of Table 2. The Figure shows that publications on each of the OIs remained well below 5000 throughout the study period. The rate of growth of HIV/AIDS literature was higher in the early stages of the pandemic, i.e. 1982–1991, as shown by the sharp increases of the number of publications. Thereafter, the rate of increase slows down to an extent of being almost constant in between 1991–1993 and 1997–1999 year-periods. The 2000–2003 year-period shows an improvement from the previous 4 two-year periods.

4.2. HIV/AIDS and opportunistic infections: Co-occurrence relations

The frequency distribution of co-occurrence of HIV/AIDS and each of the OIs is shown in Table 3. The findings reveal that *Cytomegalovirus* co-occurred with HIV/AIDS in 3871 records followed by *Pneumocystis*

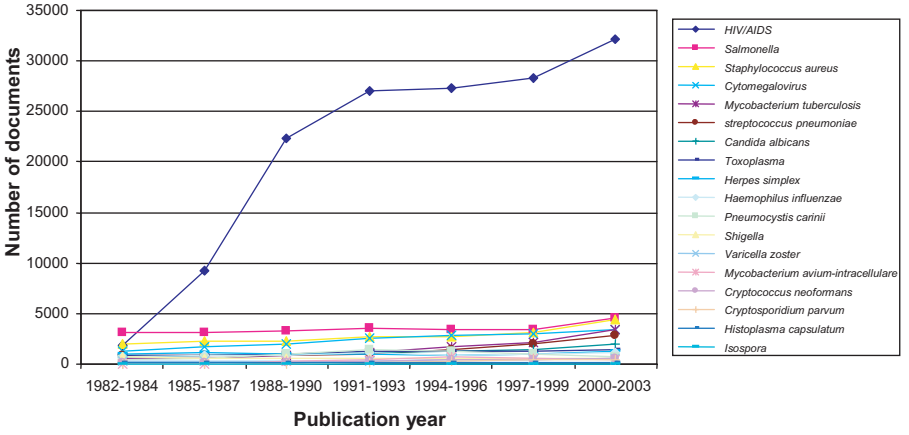

Fig. 1. Trend in research on HIV/AIDS and each OI for the period 1982–2003.

Table 3
HIV/AIDS and OIs: Co-occurrence matrix

Rank	HIV/AIDS								
1	*Cytomegalovirus*	222	370	511	694	939	910	225	3871
2	*Pneumocystis carinii*	213	340	692	943	813	545	119	3665
3	*Toxoplasma*	62	121	230	364	383	260	51	1471
4	*Mycobacterium avium-intracellulare*	0	0	142	244	465	343	72	1266
5	*Mycobacterium tuberculosis*	0	7	49	149	254	324	84	867
6	*Herpes simplex*	32	69	98	96	104	159	33	591
7	*Candida albicans*	3	7	31	58	128	155	35	417
8	*Cryptococcus neoformans*	2	21	48	69	114	113	31	398
9	*Salmonella*	5	37	46	61	75	75	27	326
10	*Streptococcus pneumoniae*	2	7	27	42	75	77	24	254
11	*Staphylococcus aureus*	2	4	23	33	61	73	21	217
12	*Varicella zoster*	2	6	18	30	53	74	15	198
13	*Cryptosporidium parvum*	0	0	0	23	40	63	12	138
14	*Histoplasma capsulatum*	1	4	8	24	24	27	15	103
15	*Haemophilus influenzae*	0	5	6	21	21	16	5	74
16	*Isospora*	3	4	4	17	24	19	1	72
17	*Shigella*	4	6	7	10	10	5	1	43
Year of publication		1982–1984	1985–1987	1988–1990	1991–1993	1994–1996	1997–1999	2000–2003	Total

carinii (3665), *Toxoplasma* (1471), and *Mycobacterium avium*-intracellulare (1266). The frequency of co-occurrence of the other OIs with HIV/AIDS was less than 1000. In the descending order, *Mycobacterium tuberculosis* ranked number five with 867 co-occurrences followed by *Herpes simplex* (591), *Candida albicans* (417), *Cryptococcus neoformans* (398), *Salmonella* (326), and *Streptococcus pneumoniae* (254). Others are *Staphylococcus aureus* (217), *Varicella zoster* (198), *Cryptosporidium parvum* (138), *Histoplasma capsulatum* (103), *Haemophilus influenzae* (74), *Isospora* (72) and *Shigella* (43).

Fig. 2 shows the trend of co-occurrence of HIV/AIDS and the individual OIs between 1982 and 2003. There is an upward trend in the number of times each of the OIs co-occurs with HIV/AIDS up till early 1990s. *Pneumocystis carinii* reaches the peak in 1991–1993 and beyond that the co-occurrence frequency starts a downward movement while *Cytomegalovirus*' frequency of co-occurrence is highest in

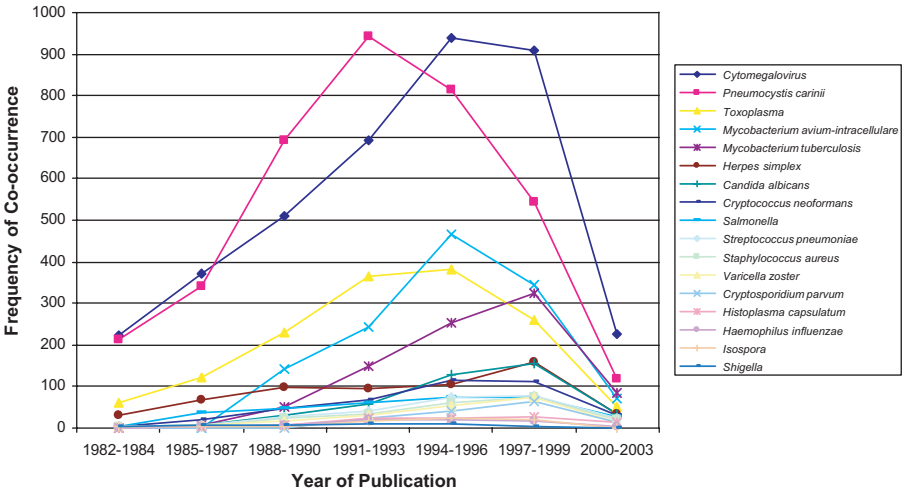

Fig. 2. HIV/AIDS and OIs: trend of co-occurrence for the period, 1982–2003.

1994–1996. Whereas *Toxoplasma* reaches its highest point at 383 in 1994–1996, the rest of the opportunistic diseases' frequency of co-occurrence continues to grow up till 1997–1999. Thereafter, the number of records in which these OIs co-appear with HIV/AIDS drops drastically.

4.3. HIV/AIDS and the opportunistic infections: Strengths of association

The strength of association is expressed as a ratio of the number of documents in which the terms M_i and M_j appear together to the occurrence frequency of term M_i multiplied by the occurrence frequency of term

Table 4
Strength of association between HIV/AIDS and OIs by year of publication, 1982–2003

	HIV/AIDS							
	1982–1984	1985–1987	1988–1990	1991–1993	1994–1996	1997–1999	2000–2003	1982–2003
Pneumocystis carinii	0.062692	0.022539	0.021436	0.024034	0.019784	0.011097	0.000622	0.014641
Cytomegalovirus	0.020258	0.008734	0.005714	0.007055	0.01112	0.009921	0.000471	0.00603
Mycobacterium avium-intracellulare	–	–	0.003116	0.004751	0.010807	0.007373	0.000362	0.004331
Toxoplasma	0.002517	0.001811	0.002454	0.00395	0.004206	0.001924	0.00006	0.001876
Cryptococcus neoformans	0.000017	0.000333	0.000584	0.000666	0.001257	0.001038	0.000051	0.000504
Mycobacterium tuberculosis	–	0.000009	0.000131	0.000716	0.001385	0.00169	0.000065	0.000483
Herpes simplex	0.000523	0.000465	0.000441	0.000357	0.000448	0.000956	0.000027	0.000328
Candida albicans	0.000007	0.000007	0.000045	0.000111	0.000468	0.000624	0.00002	0.000143
Isospora	0.000193	0.000054	0.000036	0.000244	0.000399	0.000261	0.000001	0.000132
Cryptosporidium parvum	–	–	–	0.000179	0.000239	0.000374	0.00001	0.000114
Varicella zoster	0.000008	0.000012	0.000045	0.000096	0.000242	0.000469	0.000013	0.000099
Histoplasma capsulatum	0.000007	0.000023	0.000031	0.000212	0.000198	0.00021	0.000044	0.000097
Streptococcus pneumoniae	0.000003	0.000007	0.00004	0.000067	0.000141	0.000109	0.000007	0.000045
Salmonella species	0.000005	0.000048	0.000029	0.000039	0.000061	0.00006	0.000005	0.00003
Staphylococcus aureus	0.000002	0.000001	0.000011	0.000016	0.00005	0.00006	0.000004	0.000017
Haemophilus influenzae	–	0.000003	0.000002	0.000015	0.000018	0.00001	0.000001	0.000006
Shigella species	0.000013	0.000007	0.000004	0.000006	0.000007	0.000002	0.000001	0.000003

M_j. The ranking in Table 4 shows that *Pneumocystis carinii* leads with the strength of association of $S = 0.014641$ followed by *Cytomegalovirus* ($S = 0.00603$), *Mycobacterium avium-intracellulare* ($S = 0.004331$), *Toxoplasma* ($S = 0.001876$), and *Cryptococcus neoformans* ($S = 0.000504$). *Mycobacterium tuberculosis* had a strength of association of $S = 0.000483$ while *Herpes simplex* ranked seventh with $S = 0.000328$. Others in the descending order include *Candida albicans* ($S = 0.000143$), *Isospora* ($S = 0.000132$), *Cryptosporidium parvum* ($S = 0.000114$), *Varicella zoster* ($S = 0.000099$), *Histoplasma capsulatum* ($S = 0.000097$), *Streptococcus pneumoniae* ($S = 0.000045$), and *Salmonella* ($S = 0.00003$). At the bottom of the table are *Staphylococcus aureus* ($S = 0.000017$), *Haemophilus influenzae* ($S = 0.000006$), and the *Shigella*, which was ranked last with the strength of association of ($S = 0.000003$).

The last column in Table 4 provides the ratios for the entire period of 1982–2003 and not the sum of the various individual strengths of association in that period. Thus, it can be noticed that, although *Pneumocystis carinii* and *Cytomegalovirus* had strong associations to HIV/AIDS in 1982–2003 (i.e. $S = 0.014641$ and $S = 0.00603$, respectively), their strengths of association was highest in 1982–1984. This is well illustrated in Fig. 3, which at the same time provides a vivid picture of the declining associations of OIs to HIV/AIDS. Other opportunistic diseases were less associated to HIV/AIDS during the early 1980s than they were in the late 1990s. Four of these, namely *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, *Cryptosporidium parvum*, and *Haemophilus influenzae* had no association in the early 1990s. Generally the Figure shows a decline in the strengths of association for all OIs.

4.4. Opportunistic infections: Co-occurrence relations

Table 5 presents the frequencies of co-occurrences among the opportunistic infections. The table shows that *Candida albicans* had the highest co-occurrence rate with *Staphylococcus aureus* (476) and *Cryptococcus neoformans* (183) while the frequencies of its co-appearance with each of the remaining opportunistic infections were less than 100. *Cryptosporidium parvum* had the least number of appearances with each of the other diseases. *Cytomegalovirus* appeared 578 times with *Herpes simplex* while it co-occurred in 470 records with *Pneumocystis carinii*, 406 with *Toxoplasma*, 283 with *Varicella zoster* and 132 times with

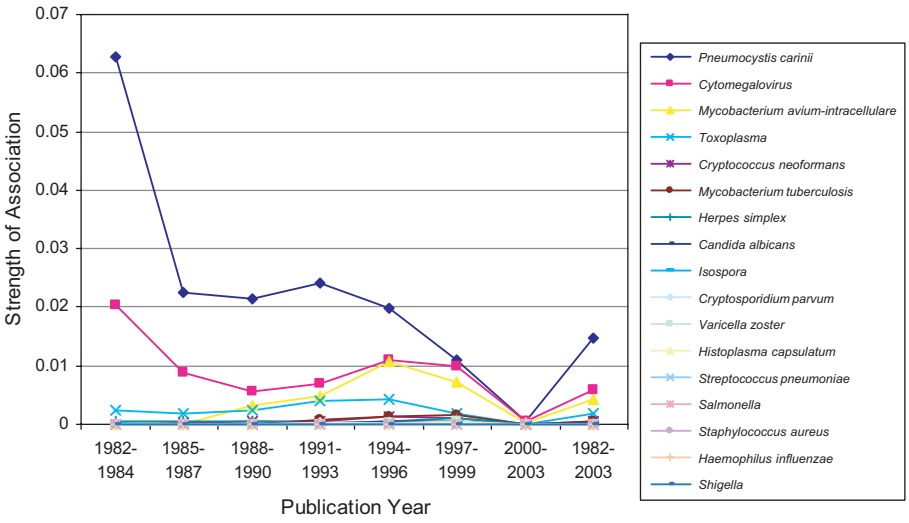

Fig. 3. HIV/AIDS-OIs: strengths of association for the period 1982–2003.

Table 5
Opportunistic Infections: Co-occurrence matrix

	Candida Albicans	*Cryptococcus neoformans*	*Cryptosporidium parvum*	*Cytomegalovirus*	*Haemophilus influenzae*	*Herpes simplex*	*Histoplasma capsulatum*	*Isospora*	*Mycobacterium avium-intracellulare*	*Mycobacterium tuberculosis*	*Pneumocystis carinii*	*Salmonella*	*Shigella*	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Toxoplasma*	*Varicella zoster*
Candida albicans	8250	183	0	11	13	3	19	1	4	20	26	33	4	476	17	7	1
Cryptococcus neoformans	183	2122	1	5	3	3	27	0	10	7	14	1	0	18	4	5	0
Cryptosporidium parvum	0	1	1217	0	0	0	0	16	2	1	4	5	2	0	0	13	0
Cytomegalovirus	11	5	0	16767	12	578	1	3	132	14	470	17	7	9	9	406	283
Haemophilus influenzae	13	3	0	12	6733	2	0	0	1	17	11	52	7	381	1343	1	4
Herpes simplex	3	3	0	578	2	7201	0	0	13	2	51	13	3	11	2	103	162
Histoplasma capsulatum	19	27	0	1	0	0	741	0	3	4	8	1	0	3	0	1	0
Isospora	1	0	16	3	0	0	0	266	0	0	3	3	0	0	0	12	0
Mycobacterium avium-intracellulare	4	10	2	132	1	13	3	0	2497	278	150	6	0	8	2	60	0
Mycobacterium tuberculosis	20	7	1	14	17	2	4	0	278	10501	21	40	4	72	31	10	4
Pneumocystis carinii	26	14	4	470	11	51	8	3	150	21	6191	14	4	8	25	313	1
Salmonella	33	1	5	17	52	13	1	3	6	40	14	24495	795	345	73	33	0
Shigella	4	0	2	7	7	3	0	0	0	4	4	795	4147	47	9	1	0
Staphylococcus aureus	476	18	0	9	381	11	3	0	8	72	8	345	47	19721	527	3	1
Streptococcus pneumoniae	17	4	0	9	1343	2	0	0	2	31	25	73	9	527	9790	4	5
Toxoplasma	7	5	13	406	1	103	1	12	60	10	313	33	1	3	4	7785	11
Varicella zoster	1	0	0	283	4	162	0	0	0	4	1	0	0	1	5	11	2693

Mycobacterium avium-intracellulare. *Haemophilus influenzae* co-appeared with *Streptococcus pneumoniae* in 1343. *Herpes simplex* recorded 162 and 103 appearances with *Varicella zoster* and *Toxoplasma*, respectively. Out of its 10,501 publications in the MEDLINE database, *Mycobacterium tuberculosis* co-occurred in 278 publications with *Mycobacterium avium-intracellulare* and less than 100 times with each of the remaining OIs. There were several cases of zero frequencies of term co-occurrence.

4.5. Opportunistic infections: Strengths of association

The strengths of association values, shown in Table 6, show that the strongest link was witnessed between *Haemophilus influenzae* and *Streptococcus pneumoniae* with a score of $S = 0.027363$. Equally significant scores were witnessed between *Candida albicans* and two other OIs, namely, *Cryptococcus neoformans* ($S = 0.001913$) and *Staphylococcus aureus* ($S = 0.001393$). Other fairly high strengths of association were between *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* ($S = 0.002947$), *Pneumocystis carinii* and *Mycobacterium avium-intracellulare* ($S = 0.001455$), *Herpes simplex* and *Varicella Zoster* ($S = 0.001353$), and *Staphylococcus aureus* and *Haemophilus influenzae* ($S = 0.001093$). *Cytomegalovirus* recorded strong links with four OIs, i.e. *Herpes simplex* ($S = 0.002767$), *Pneumocystis carinii* ($S = 0.002128$), and *Toxoplasmosis* ($S = 0.001263$) and *Varicella Zoster* ($S = 0.001774$). It can be noticed that a disease generates the strength of association equalling to one (1) when the S is calculated against the same disease.

Table 6
Opportunistic diseases: strengths of association matrix

	Candida Albicans	*Cryptococcus neoformans*	*Cryptosporidium parvum*	*Cytomegalovirus*	*Haemophilus influenzae*	*Herpes simplex*	*Histoplasma capsulatum*	*Isospora*	*Mycobacterium avium-intracellulare*	*Mycobacterium tuberculosis*	*Pneumocystis carinii*	*Salmonella species*	*Shigella species*	*Staphylococcus aureus*	*Streptococcus pneumoniae*	*Toxoplasma*	*Varicella zoster*
Candida albicans	1	0.001913	0	0.000001	0.000003	0	0.000059	0	0.000001	0.000005	0.000013	0.000005	0	0.001393	0.000004	0.000001	0
Cryptococcus neoformans	0.001913	1	0	0.000001	0.000001	0.000001	0.000464	0	0.000019	0.000002	0.000015	0	0	0.000008	0.000001	0.000002	0
Cryptosporidium parvum	0	0	1	0	0	0	0	0.000791	0.000001	0	0.000002	0.000001	0.000001	0	0	0.000018	0
Cytome galovirus	0.000001	0.000001	0	1	0.000001	0.002767	0	0.000002	0.000416	0.000001	0.002128	0.000001	0.000001	0	0	0.001263	0.001774
Haemophilus influenzae	0.000003	0.000001	0	0.000001	1	0	0	0	0	0.000004	0.000003	0.000016	0.000002	0.001093	0.027363	0	0.000001
Herpes simplex	0	0.000001	0	0.002767	0	1	0	0	0.000009	0	0.000058	0.000001	0	0.000001	0	0.000189	0.001353
Histoplasma capsulatum	0.000059	0.000464	0	0	0	0	1	0	0.000005	0.000002	0.000014	0	0	0.000001	0	0	0
Isospora	0	0	0.000791	0.000002	0	0	0	1	0	0	0.000005	0.000001	0	0	0	0.00007	0
Mycobacterium avium-intracellulare	0.000001	0.000019	0.000001	0.000416	0	0.000009	0.000005	0	1	0.002947	0.001455	0.000001	0	0.000001	0	0.000185	0
Mycobacterium tuberculosis	0.000005	0.000002	0	0.000001	0.000004	0	0.000002	0	0.002947	1	0.000007	0.000006	0	0.000025	0.000009	0.000001	0.000001
Pneumocystis carinii	0.000013	0.000015	0.000002	0.002128	0.000003	0.000058	0.000014	0.000005	0.001455	0.000007	1	0.000001	0.000001	0.000001	0.00001	0.002033	0
Salmonella species	0.000005	0	0.000001	0.000001	0.000016	0.000001	0	0.000001	0.000001	0.000006	0.000001	1	0.006222	0.000246	0.000022	0.000006	0
Shigella species	0	0	0.000001	0.000001	0.000002	0	0	0	0	0	0.000001	0.006222	1	0.000027	0.000002	0	0
Staphylococcus aureus	0.001393	0.000008	0	0	0.001093	0.000001	0.000001	0	0.000001	0.000025	0.000001	0.000246	0.000027	1	0.001438	0	0
Streptococcus pneumoniae	0.000004	0.000001	0	0	0.027363	0	0	0	0	0.000009	0.00001	0.000022	0.000002	0.001438	1	0	0.000001
Toxoplasma	0.000001	0.000002	0.000018	0.001263	0	0.000189	0	0.00007	0.000185	0.000001	0.002033	0.000006	0	0	0	1	0.000006
Varicella zoster	0	0	0	0.001774	0.000001	0.001353	0	0	0	0.000001	0	0	0	0	0.000001	0.000006	1

5. Discussions

An estimated 148,220 records on HIV/AIDS were analysed between 1982 and 2003. Comparatively, the 1991–1999 period yielded more publications than 1982–1990. Whereas the period of 1982–1990 yielded 33,462 records, 1991–1999 had 82,599 publications, which is more than double. Similar findings have been documented in previous studies. For example, Pratt (1992) analysed a cumulative total of 29,077 AIDS records between 1981 and 1990, although this figure did not represent the total number of AIDS-related items in the MEDLINE database (FitzSimons, 1993; Pratt, 1993). On his part, Elford (cited in FitzSimons, 1993) estimated some 33,000 publications on HIV/AIDS in the same database between 1981 and 1990. Previous studies have indicated that the growth of AIDS literature has been exponential in nature and that this growth rate matched the number of AIDS cases (Macias-Chapula, Rodea-Castro, & Narvaez-Berthelemot, 1998). This pattern was, however, not identified in this study.

Whereas research on individual OIs has shown an upward trend when we consider the growth of related literature, Table 2 shows that it still remains far below that of AIDS. This can be attributed to the heavy funding geared towards AIDS research, most probably because of the disease's devastating effect on the social, economic and political development. Secondly, its cure is still far from being discovered, a situation that may have called for continued financial disbursements. This has culminated in the establishment by UNAIDS of the Global Fund to fight the disease. The Global Fund is geared towards financing the fight against not only AIDS, but also tuberculosis and malaria (UNAIDS, 2004). This may also explain the considerable number of publications on *Mycobacterium tuberculosis*.

Summers and Kates (2004) estimate that the US government has invested approximately $150 billion for both domestic and international HIV/AIDS programs since 1982. Funding categories for which this amount of money has been invested are care (health and support services), cash and housing assistance, research, prevention and global or international programs. The authors estimate that 16% of the federal funding for the fiscal year 2004 has been allocated to the research activities. The Global Fund's disbursements to different world geographic regions and by grant agreements for year 2004 is projected to be a total of $280,267,086 (UNAIDS, 2004). In contrast, except for an estimated $320,000 awarded to Digene Corporation to develop a new generation of tests for the diagnosis of *Herpes simplex* virus (HSV) (Digene Corporation, 2001), there were no immediate data on the funding statistics on other OIs.

Concerning the co-occurrence of HIV/AIDS and OIs, Tables 3 and 4 and Figs. 2 and 3 show that there was high co-occurrence rate and strength of association between the two in the early years of the HIV/AIDS epidemic, i.e. between 1980 and 1985. Fig. 2 reveals that the co-occurrence trend reversed and thereafter the co-occurrence rate in Table 4, and strengths of association, shown in Fig. 3, continued to decline up to year 2003. Fig. 3 reveals that *Pneumocystis carinii*'s and *Cytomegalovirus*' associations with HIV/AIDS have declined with time from $S = 0.014641$ and $S = 0.00603$ in 1982–1984 to $S = 0.000622$ and $S = 0.000471$ during the 2000–2003 period, respectively. This accounts for 2253% decrease in the case of *Pneumocystis carinii* and 1180% for *Cytomegalovirus.* Also affected is the *Mycobacterium avium* complex disease.

This kind of scenario has been attributed to the use of anti-HIV drugs (New Mexico AIDS Education & Training Center, 2003). In the early years of the AIDS epidemic, OIs caused a lot of sickness and deaths. However, once people started taking combination antiviral therapy, a lot fewer people got OIs. Cohen (2000a), too, notes that through effective treatments for *Pneumocystis carinii pneumonia* (*PCP*) and HIV, the PCP rates declined drastically in the late 1990s in developed countries. Even in the poorest countries, "access to anti-HIV drugs and formula has been made cheaper and easier through the largesse of donors, discounts from industry, new trade laws and the tenacity of individual clinicians" (Cohen, 2000b).

Generally, remarkable progress has been made in improving the quality and duration of life for HIV-infected persons in the industrialized world since AIDS was first reported. The Centers for Disease Control and Prevention (CDC) (2002) reports that improved quality and duration of life during the first AIDS

decade "occurred because of improved recognition of opportunistic disease processes, improved therapy for acute and chronic complications, and introduction of chemoprophylaxis against key opportunistic pathogens".

During the last decade there was extraordinary progress in the development of highly active antiretroviral therapies (HAART), which have greatly reduced the incidence of OIs and extended life substantially (CDC, 2002). Not only has the incidence of OIs reduced in HIV/AIDS immune-compromised persons, there has been a reduction also in morbidity and mortality associated with the diseases (Palella et al., 1998). Palella et al. (1998) observe that "the incidence of any of the three major opportunistic infections (i.e. *Pneumocystis carinii pneumonia*, *Mycobacterium avium complex disease*, and *cytomegalovirus retinitis*) had declined from 21.9 per 100 person-years in 1994 to 3.7 per 100 person-years by mid-1997". With this kind of trend, we should expect the presence of OIs in persons infected with HIV to decrease further considering that many nations are advocating for the free provision of anti-HIV drugs.

Table 2 shows that there were no descriptors for *Mycobacterium avium-intracellulare* and *Cryptosporidium parvum* on the first two and three periods of years, respectively. The co-occurrence matrices in Tables 3 and 4 show similar findings on *Mycobacterium avium-intracellulare*, *Cryptosporidium parvum*, *Mycobacterium tuberculosis*, and *Haemophilus influenzae*. This may be due to the fact that NLM did not create such MeSH terms until 1988 and 1991, approximately. A similar situation happened with the creation of the HIV/AIDS descriptor around 1982. The first HIV/AIDS publication, according to this study, was published in 1982 yet HIV/AIDS was clinically diagnosed in the period October 1980–May 1981 (Begley, Check, Wingert, & Conway, 2001; Konforti, 2001; National Institute of Allergy and Infectious Diseases NIAID, 2003). A possible explanation underlying such time lapse between the discovery of the disease and the publication of literature on the respective diseases are well illustrated in Chan, Jin, Rousseau, Vaughan, and Yu (2003). In their study of *Newspaper coverage of SARS*, the authors argue that "It is just human that the meaning of new phenomena is not immediately clear, and that it takes a whole process of understanding before the full significance of the new phenomena becomes clear". This may apply to database indexers, too. Seemingly, it takes some time before a disease's descriptor is formulated.

The rankings of OIs in relation to HIV/AIDS in Table 3 and Fig. 2 shows that *Pneumocystis carinii*, *Cytomegalovirus*, *Mycobacterium avium-intracellulare*, *Toxoplasma*, *Mycobacterium tuberculosis* and *Herpes simplex* appeared more commonly in HIV/AIDS records. These infections exhibited strong associations as shown in Table 4 and Fig. 3. Ranking number one in Table 4 is *Pneumocystis carinii*, showing that the infection is the most common in persons with HIV/AIDS. According to Brookmeyer and Gail (1994, p. 10), *Pneumocystis carinii* pneumonia (PCP) is common in all risk groups and accounts for about half of all AIDS-defining conditions. The UNAIDS (1998, 4), too, reports that PCP is the "most frequent HIV-associated opportunistic infection in industrialized countries". The second most common infection, according to the findings of this study, is *Cytomegalovirus* followed by *Mycobacterium avium-intracellulare*, *Toxoplasma*, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Herpes simplex*, and Candidiasis in that order. Just like in the case of *Pneumocystis carinii*, almost everyone with HIV tests positive for *Cytomegalovirus* (*CMV*) (New Mexico AIDS Education & Training Center, 2003). Infections that are rarely linked to HIV/AIDS include *Shigella*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Salmonella*.

It can also be seen that the order of ranking of the infections in Table 3 is different from that in Table 4. For instance, whereas *Cytomegalovirus* leads the pack followed by *Pneumocystis carinii* in Table 3, the order reverses in Table 4. *Toxoplasma* and *Mycobacterium avium-intracellulare* have also changed positions. *Cryptococcus neoformans* has jumped from position 8 in Table 3 to position 5 in Table 4. *Mycobacterium tuberculosis* has moved down one step to position 6 in Table 4 just as *Herpes simplex* and *Candida albicans*. It can be seen that except for the *Shigella* viruses, which maintained the same position, all the other infections were affected. This can well be explained by Krsul's (2002) observation that "two keywords that appear infrequently in the database but always appear together will have larger strength values than keywords that appear many times in the database almost always together".

The co-occurrence of terms among the OIs themselves shows that the highest frequency of co-occurrence was witnessed between *Haemophilus influenzae* and *Streptococcus pneumoniae* (i.e. 1343). Their strength of association value was also the highest ($S = 0.027363$). Their high frequency of co-occurrence and association value can be attributed to the fact that they are both common causative agents of respiratory tract infections (Jones & Karlowsky, 2002). Significant frequencies of co-occurrences were also witnessed between *Candida albicans* and *Staphylococcus aureus* (476) and between *Candida albicans* and *Cryptococcus neoformans* (183). *Cytomegalovirus* was the most common, having co-appeared with *Herpes simplex* (578), *Pneumocystis carinii* (470), *Toxoplasma* (406), *Varicella zoster* (283), and 132 times with *Mycobacterium avium-intracellulare*. Some of these co-occurrences among the OIs were due to two or more of the diseases being analyzed in one HIV-based publication. Arguably, therefore, the fact that two or more infectious diseases can be found in an HIV immune compromised patient, may not be proof enough that they are medically related or associated. It is, however, advisable that a medical analysis be conducted to determine the relatedness of one OI to the other. Apart from these OIs being either bacterial or micro-bacterial, or fungal, or protozoal, and or viral infections, we were unable to conclusively establish their inter-relationships in this study.

6. Conclusion and recommendations

The purpose of this work was to measure the strength of association between HIV/AIDS and various purposefully selected opportunistic diseases using a uniform search strategy. It follows therefore that the collected data may not be wholly representative of the research activities that have been conducted on these diseases. Further studies are recommended to analyse AIDS literature, in other sources such as the mass media, which is not indexed in the MEDLINE database.

It is noteworthy observing that there are significant differences in the occurrence of OIs in AIDS patients in different regions. For example, whereas *Pneumocystis carinii*, *Mycobacterium avium intracellulare* and *Histoplasma capsulatum* are relatively the most common infective agents in Europe and/or North America (Williams, 1991), *Tuberculosis* kills more HIV-infected people in Africa than any other AIDS-related disease while it remains rare in AIDS patients in the United States and Europe (Cohen, 2000a). It is therefore necessary to measure the strengths of association of HIV/AIDS and OIs in individual geographic regions. By so doing, appropriate strategies may be developed for AIDS patients.

This notwithstanding and in conclusion, we found that the most common OIs in persons with HIV/AIDS exhibited strong relations of association with the disease. These infections are:

- *Candidiasis*, a fungal infection of the mouth, throat, or vagina which occurs even with fairly high T-cells;
- *Cytomegalovirus* (CMV), a viral infection that causes eye disease that can lead to blindness and occurs mostly when the T-cell count is under 50;
- *Herpes simplex viruses*, which causes oral herpes (cold sores) or genital herpes and whose outbreaks can be much more frequent and more severe in HIV infected persons. They can occur at any T-cell count;
- *Mycobacterium avium complex* (MAC or MAI), a bacterial infection that can cause recurring fevers, general sick feelings, problems with digestion, and serious weight loss and occurs when the T-cell count is under 75;
- *Pneumocystis carinii pneumonia* (PCP), a fungal infection that can cause a fatal pneumonia and occurs when T-cell count is under 200;
- *Toxoplasmosis* (Toxo), a protozoal infection of the brain and occurs when T-cell count is under 100;
- *Tuberculosis* (TB), a bacterial infection that attacks the lungs, and can cause meningitis and occurs at any T-cell count.

Wormell's (1998) observation that trends and developments in society, science and business can be traced through the informetric analyses of databases forms a strong argument for the use of informetrics techniques in LIS research. In her words,

> "The ability to retrieve, organize and store information from printed and electronic sources will no longer be regarded as the only basic concept of library and information service. Access to information itself today does not signify either competitive advantage or guarantee the feeling of being informed, neither in the research nor the business environment. The sophisticated value of online information provision is not to use the databases only for finding facts and accessing documents, but to tap the unique items of useful information, the nuggets of knowledge and (by synthesis and/or analysis) extract the 'searched pattern' in the raw data" (Wormell, 2000, 133).

Results of the current study, we believe, have implications for the indexers of information materials, too, especially in cross-referencing. Supposing that the highest S value between the highest-ranking OI (i.e. *Pneumocystis carinii*—PCP) and HIV/AIDS was 0.999654, it would have meant that wherever HIV/AIDS was a topic of discussion, there was an equal chance that PCP was also discussed alongside it. Put in other words, wherever PCP is diagnosed in patients, there are high chances that the said patient would be suffering from HIV/AIDS. Hence, the indexer would be advised to make see and/or see-also cross-references to HIV/AIDS materials when indexing PCP materials and vise versa.

Finally, we strongly concur with previous researchers that an informetric analysis of database literature, using a co-word analysis method, to determine a disease's relatedness to pathogens associated with it, is feasible.

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