

Review Article

Emergent of New Geriatric Population: HIV, Aging and Challenges of Care and Treatment

Massod Vadiee*

Queen Mary, University of London, UK

***Corresponding author:** Massod Vadiee, Queen Mary, University of London, UK**Received:** October 27, 2017; **Accepted:** December 08, 2017; **Published:** December 15, 2017**Abstract**

With the introduction of the Highly Active Antiretroviral Therapy (HAART) the survival rate among the older adults (age 50 and over) infected with HIV/AIDS has risen dramatically. The improved survival is expected to continue over the next decades that will create a considerable demographic shift in the proportion of HIV infected individuals living into their late senior age. The impressive survival rate on the other hand has resulted in increased frequency of non-HIV-related co morbidities, (e.g.; cardiovascular and metabolic syndromes, cancer, neuro-cognitive conditions) as well as age-related geriatric syndromes. Several unanswered questions has been put set forward regarding the role that HIV might play as an age accelerator either through multi-faceted mechanisms associated with the complex aging process itself or possibly through risk factors commonly observed in chronic conditions. While, strong evidences about the role of perpetual inflammation, immune dysfunction and immunescence continue to emerge as one of the many plausible explanations , the complexity of assessing each individual contributing factor such as; HIV, HAARTS effects, immune senescence, inflammation is compounded by the lack of reliable biological markers impeding any investigations that could reveal the degree by which the aging process, HIV infection or HAARTS toxicity as culprits for co-morbidity and age accelerations in the elderly population. While The future basic research is needed into biology of aging, as well as translational research in therapeutic approach in HIV co-morbidities will be instrumental in for reaching better care outcomes in this population, the current evidence strongly indicates that in order to address age-related or co-morbid complications, pharmacological treatment toxicity, adherence as well as psycho-social issues, a more unifying and age-specific screening and chronic care and assessment guidelines such as Comprehensive Geriatric Assessment (CGS) can play a major role in early detection, initiation of prudent treatment and a successful healthy aging in this population.

Methods: We conducted a Pub-Med and PLOS systematic content review of existing peer-reviewed research and reports on HIV and aging and identified 1500 articles that were published between 2005 and 2014. The inclusion criteria were those publications that were focused on aging and HIV infection's care and treatment among older populations (aged 50 and over). Based on the review of these publications, the search terms were further refined to "HIV/AIDS and aging" and subsequently to HIV/AIDS and Treatment and Care in order to capture additional articles. Approximately 125 publications were identified that met our criteria. A subset of these articles was selected for the purpose of this review.

Conclusion: While, the Highly Active Antiretroviral Therapy (HAART) has improved the survival rate dramatically, it has resulted in rise of elderly population surviving well into their late senior years. As this population ages, the prevalence of age related, inflammatory and immune based co-morbidities will increase, therefore requiring a better understanding of the complex aging process as and the underlying mechanisms involving immunescence, inflammation and their possible impact on aging acceleration and age related conditions. Today, limited controlled investigation has been performed on the older HIV-infected adults, and few studies have comprehensively examined the spectrum of co-morbid conditions and geriatrics syndrome in older HIV-infected adults. As we continue to investigate the complex interaction between aging on HIV infection and search for better therapeutics, the complex medical and psychological needs of older population infected with HIV should also be addressed. As the health delivery care systems and the geriatricians begin embrace changes that reflect the unmet needs of an older HIV infected population, the proven and cost and

effective principles of long term and chronic care model (ex; comprehensive geriatric assessments) should be embraced in order to foster a better health outcome among this vulnerable population.

Keywords: Aging; HIV/AIDS; Immunity; immunescence; HAART Toxicity; Co-morbid Conditions; Geriatrics Assessment; Care Guidelines; Health care management

Introduction

HIV, Aging and the emergent of a geriatrics population

Currently, with half of the HIV-infected persons in the United States surviving well beyond the age of 50 years of age by year 2015, the Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and the Protease Inhibitors (PIs) in combinations frequently referred to as 'HAART' (*highly active antiretroviral therapy*) have shown to have a favorable impact on curtailing the HIV-associated mortality [1,2]. In the resource limited regions of Sub-Saharan, South Africa and Asia the incident of HIV infection among the older population has increased by 14.3% of HIV-infected adults surviving well beyond the age 50 [3,4]. This impressive improvement in life expectancy is largely the result of not only our ability to clinically prevent and manage co-morbidities (e.g.; cardiovascular and metabolic syndromes, cancer and neuro-cognitive, etc), but also due to our capability in prevention of events after ART administration and conditions generally considered to be none Aids-related [5-7]. In the United States, the older patients with HIV represent an impressive 20% to 25% of the entire HIV population, and while similar demographic trends in Europe in order to enhance screening, preventive and health care delivery needs imposed by this growing and vulnerable population, resources have begun to strain the health delivery systems [7-10]. Today, while systematic demographic data on the older HIV infected individuals remains inadequately researched and inconclusive, it is however clear that a growing geriatric population afflicted with a ranges of chronic and long term conditions will continue to expand as a healthcare burden and challenge the physicians and care provider [11-13].

HIV, Immunity and accelerated aging

While, the increasingly common HIV associated Non-AIDS conditions are associated with aging and chronic inflammation, the aging phenomenon, the HIV infections and the increased risk for HIV-related co-morbidities among older patients in studies have been describes as a complex, multifaceted interplay between aging, the role of HIV related inflammation and repetitive induction -exhaustion of the immune system that leads to an oxidative stress mitochondrial dysfunction has been postulated as the possible drivers behind the onset of co-morbid conditions and accelerated aging [12-14]. Additionally, while It remains to be seen whether people with HIV infection develop these conditions earlier in their life course or are simply at greater risk of developing aging associated conditions at ages observed among those without HIV infection, explanations has also been set forward about the on the complex interplay between the aging process, the perpetual state of repetitive inflammatory cascades that propagate into what is referred to as state of *immunescence* or immune dysfunction, linking the premature aging in HIV/AIDS to mechanisms involving either telomerase inhibition or the HIV/AIDS

therapeutic side effects [14,15]. Today, while it is almost impossible to successfully separate factors influencing or impacting the aging process that bring about the complex, multi-morbid illness in older HIV patients, it is also often necessary to utilize validated indices to better assess and predict specific interventions and outcomes among a variety of patient [16,17]. New categories of stressors linked to a synergetic chronic immune activation-exhaustion response have been implicated as possible contributors to the alterations in numbers and the performance of biological markers (i.e. ;T-lymphocyte, Interleukin IL – 6) and likely associated with diseases and late-life changes such as age acceleration associated, early mortality, therefore In the future, the integration of laboratory and clinical measures, and emerging robust biomarkers are likely to be more relying on simple, traditional, HIV-specific variables such as CD4 count or viral load [18-20]. It is understood that the unifying mechanism that appear lead to greater incidence of disease and frailty in persons with HIV appear to be the Immune senescence, inflammation and hypercoagulability , therefore the future research should focus on addressing the lack of animal models that can appropriately reproduce complexities of HIV, ART, aging, multi-morbidity and functional outcomes of relevance indicate that human studies and future improve our understanding aging and HIV infection with more well designed human studies on biology of aging to aid us in discovery of a new generations of validated and robust independent biomarkers [20-22]. Additionally, more basic science studies needed on the precise nature of how cell signaling causes and increase senescence memory CD8 T-cells and reduction in T-cell regeneration and decline in naive T cells and ratio of CD4⁺ to CD8⁺ cells which collectively leads to global features of what is known as immunesence and a higher than normal risk among the long term treated older HIV patients for metabolic and cardiovascular, cancer, and end-organ diseases [23-25]. The future research HIV and aging will also include more rigorous research into the biology of inflammation and disease development, the identification and validation of new independent biomarkers as well as clinically relevant various interventions that could enable clinicians to each clinical outcomes and preserve function in a populations challenged with complex medical needs [26,27]. The long term success in the clinical management of global features of immune dysfunction particularly in management inflammation, chronic endotoxaemia, residual viremia, telomere attrition as well as future success in development of more efficacious therapeutics are all dependent on our insight into mechanisms that lead to aging, innate and adaptive immunity, the role of chronic viruses on inflammation and immune senescence [26-30].

Aging and harts toxicity

The studies suggest that while virologic response among older and younger HIV infected patients are similar, the older patients display a more sluggish immunological reaction to HAART, thus making the complex pharmacological management of HIV a key obstacle that

can only be overcome by understanding the mechanism involving the biology of aging and in particular immunological breakdown among older HIV patients [30-35]. To successfully address the challenges of HAARTS toxicity among older HIV infected population, important questions regarding other key compounding factors among older HIV infected population such as; late diagnosis, lower viral-load, higher risk for end-organ diseases, frailty as well as poly-pharmacy should also be investigated [34-36]. Further exploration of un-answered questions related to persistent inflammation, HAART toxicity and the plausible relationship between immunodeficiency and chronic effects of specific oncogenic infections will become more possible if broader aspects of immune dysfunction and immunescence among older people with HIV is more thoroughly understood [37-39]. The typical clinical presentation of an older HIV patients display a more sluggish humoral immunity, a lower CD4 (+) T cell counts, higher viral load, more symptoms at diagnosis, and a tendency for rapid progression with more co-morbid conditions, indicating that the complex aging process that synergistically plays part between HIV infections, immune system, among elderly with HIV infection [40-45]. The pharmacological management of HAARTS regimens in older HIV infected patients continue to requires the careful risk assessment for class selection, timing and potential drug-drug interactions as we continue our search *on ways* enhancing tolerability and individualization of therapeutic treatment options with d4T+3TC+, NNRTI, and AZT+3TC+NNRTI therapeutics [46-53]. Finally, the treatment and care of often frail with a less robust immune system older HIV-infected patients remain compounded by a synergism between aging, HIV infection and ongoing immunodeficiency that contribute to age-associated end-organ dysfunction and non-AIDS-defining co-morbidities (i.e. dyslipidemia, metabolic syndrome, osteoporosis, and neurocognitive disorder) therefore, making more longitudinal investigational research in aging a priority for developing in age sensitive age-specific guidelines in order to reduce burden of chronic care the resource challenged health care settings [54-64].

Adherence, chronic care and case comprehensive geriatric assessment

The maintenance of an optimal medication adherence among older population has been a real challenge due the age related hepatics decline functions, co-morbidities, frailty, and cognitive decline often compounded by lack of age specific studies in areas of medication complexity, cost, and side effects in this vulnerable population [65-70]. While some studies have discounted age as having little or no associations with improved adherence, many older individuals with suboptimal adherence to treatment continue to remain clinically at risk for additive impact and or inadvertent disease progression, therefore information the extent non-adherence remains crucial in a successful treatment [71-74]. New investigations on adherence predictors including; medication complexity, co-morbidities, cognitive impairment as well as relevant information on social and cultural indices needed in older to explore the real extent of non-adherence and reduce suffering and help older adults with HIV to experience a healthy successful aging [75-81]. The limited data on older HIV patients HAART tolerability and non-disclosure about chief complains and symptoms continues to be among the key challenges facing the elder care specialists, geriatricians when forging ahead with a clinically sound and patient-centered care [82-85].

The medical and psycho-social needs of HIV patients have always been diverse and requiring service and attention of verity of care providers and specialist across a number of different health settings. Moreover, HIV infection among in older population often challenges by the development of high rates of physical and mental health co-morbidities in this population, therefore implementation of a more age appropriate HIV screening and prevention that is capable of responding to this growing emerging geriatric population is paramount [86-92]. Among a variety of care models aimed at delivering care for elderly population has been designed and put in practice, the Comprehensive Geriatric Assessment (CGS) has for the most part been successful in attempting to organize geriatric medicine service around a multidisciplinary care of older adults by a systematic evaluation scheme often led by geriatrician that will focus on complex medical, psychological and functional deficits (ex; falls, cognitive status changes, incontinence) a prioritization care approach to determine who might benefit by medical and rehabilitation efforts [91-95].

A number of trails have found CGS to be to highly cost effective and was adapted in USA in 1979 to identify, assess, and treat frail, disabled older patient who were at risk for institutionalization and did not to benefit from usual care [96-98]. Although, factors such as; organizational diversity, complexity of geriatric evaluation, and the difficulty in replicating successful single-site studies has limited the universal implementation of CGA, nonetheless the CGA shown to be cost effective and an efficient model of care for elderly with multiplicity of long term cumulative injury functional, cognitive and psychosocial needs including HIV [98-102].

Conclusion

The major improvements in antiretroviral therapy have resulted in an increasing proportion of individuals with HIV infection are living into older age. This prolonged survival is accompanied by an increased frequency of non-HIV-related co-morbidities and age-related geriatrics syndromes. Currently, the precise nature of the complex dynamic between HIV, the complex aging process and the immunescence are still not well understood. While, we have been able to better protect patients form the pharmacologically related toxicities, more Controlled trials needed on impact HAARTS and co-morbid conditions on aging enhance our treatment modalities and improve the associated HAARTS toxicities in older HIV populations and in older patients. Future research will also likely focus on reliable and novels biomarkers in disease progression and investigate factors associated with a more rapid course of HIV infection in older patients in order. Our ability to effectively manage the HAARTS toxicity, co-morbidities and poly-pharmacy is lagging due to the fact that considerable research disparity that currently exist in the area of in prevention and treatment guidelines strategy between the older compared with younger HIV patients. The current epidemiological shift in HIV epidemic and the subsequent rise of a new HIV infected older populations will be living with a variety of age and treatment-related chronic conditions will require new commitments to capacity building within the health care delivery systems and the input of geriatricians knowledgeable and aware of the clinical and psychosocial issues particular to this group. Furthermore, the future of care of the elderly with HIV is now more based on successful healthy aging

rather than just survival. To better address the future care challenges for this growing population, the service delivery options should accommodate for the complex care needs among this population with overlapping effects of multi-morbidity and aging. The care providers and geriatricians also need to enhance their diagnostic and care guidelines by more vigorously embracing the proven tenets of Comprehensive Geriatrics Assessment and to address the challenges regarding age sensitive screening, adherence, HAARTS toxicity and identify common pathways of in offering more personalized care preventing injury functional and cognitive decline in elderly with HIV infection.

References

- Cohort C. Antiretroviral Therapy. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008; 372: 293–299.
- CDC. HIV/AIDS among persons aged 50 or over. 2010.
- Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bull World Health Organ*. 2010; 88:847–853.
- Hontelez JA, Lurie MN, Newell ML, Bakker R, Tanser F, Barnighausen T, et al. Ageing with HIV in South Africa. *AIDS*. 2011; 25: 1665–1667.
- Liu H, Lin X, Xu Y, Chen S, Shi J, Morisky D. Emerging HIV epidemic among older adults in Nanning, China. *AIDS Patient Care STDS*. 2012; 26: 565–567.
- Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related co morbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011; 53: 1120–1126.
- Effros RB, Fletcher CV, Gebo K, Jeffrey BH, William RH, Frances McFarland H, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. *Clin Infect Dis*. 2008; 47: 542–553.
- Centers for Disease Control and Prevention. HIV Surveillance Report. 2011.
- Vivian lida Avelino-Silva, Yeh-Li Ho, Thiago Junqueira Avelino-Silva, Sigrid De Sousa Santos. Aging and HIV infection. *Ageing Res Rev*. 2011; 10: 163–172.
- Vance DE, Childs G, Moneyham L, McKie-Bell P. Successful aging with HIV: a brief overview for nursing. *J Gerontol Nurs*. 2009; 35: 19–25.
- Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ*. 2009; 338: a3172.
- Nasi M, Pinti M, De Biasi S, Gibellini L, Ferraro D, Mussini C, et al. Aging with HIV infection: a journey to the center of inflammAIDS, immunosenescence and neuroHIV. *Immuno Lett*. 2014; 162: 329–333.
- Le Saux S, Weyand CM, Goronzy II. Mechanisms of immunosenescence: lessons from 2-models of accelerated immune aging. *Ann N Y Acad Sci*. 2012; 1247: 69–82.
- Ferrando-Martínez S, Ruiz-Mateos E, Romero-Sánchez MC, Muñoz-Fernández MA, Viciano P, Genebat M, et al. HIV infection-related premature immunosenescence: high rates of immune exhaustion after short time of infection. *Curr HIV Res*. 2011; 9: 289–294.
- Hearps AC, Angelovich TA, Jaworowski A, Mills J, Landay AL, Crowe SM. HIV infection and aging of the innate immune system. *Sex Health*. 2011; 8: 453–464.
- Dock JN, Effros RB. Role of CD8 T Cell Replicative Senescence in Human Aging and in HIV mediated Immunosenescence. *Aging Dis*. 2011; 2: 382–397.
- Levy JA, Ory MG, Crystal S. HIV/AIDS interventions for midlife and older adults: current status and challenges. *J Acquir Immune Defic Syndr*. 2003; 33: 59–67.
- Levy BR, Ding L, Lakra D, Kosteads J, Niccolai L. Older persons' exclusion from sexually transmitted disease risk-reduction clinical trials. *Sex Transm Dis*. 2007; 34: 541–544.
- Dalli J. How to make healthy ageing a reality. 2012.
- Schmid GP, Williams BG, Garcia-Calleja JM, Miller C, Segar E, Southworth M, et al. Unexplored Story of HIV and Ageing. *Bulletin of the World Health Organization*. 2009; 87: 162–162.
- Bhavan KP, Kampalath VN, Overton ET. The Aging of the HIV Epidemic. *Curr HIV/AIDS Rep*. 2008; 5: 150–158.
- Martin CP, Fain MJ, Klotz SA. The older HIV-positive adult: a critical review of the medical literature. *Am J Med*. 2008; 121: 1032–1037.
- Kearney F, Moore AR, Donegan CF, Lambert J. The ageing of HIV: implications for geriatric medicine. *Age and Ageing*. 2010; 39: 536–541.
- Sahin E, Colla S, Liesa M, Moslehi J, Müller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature*. 2011; 470: 359–365.
- Nakagawa F, May M, Phillips A. Life expectancy living with HIV: recent estimates and future implications. *Curr Opin Infect Dis*. 2013; 26: 17–25.
- Martin GE, Gouillou M, Hearps AC, Angelovich TA, Cheng AC, Lynch F, et al. Age-associated changes in monocyte and innate immune activation markers occur more rapidly in HIV infected women. *PLoS One*. 2013; 8: e55279.
- Salvioli S, Monti D, Lanzarini C, Conte M, Pirazzini C, Bacalini MG, et al. Immune system, cell senescence, aging and longevity – inflamm-aging reappraised. *Curr Pharm Des*. 2013; 19: 1675–1679.
- Beswick M, Pachnio A, Lauder SN, Sweet C, Moss PA. Antiviral therapy can reverse the development of immune senescence in elderly mice with latent cytomegalovirus infection. *J Virol*. 2013; 87: 779–789.
- Lutz CT, Quinn LS. Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. *Aging (Albany, NY)*. 2012; 4: 535–546.
- Grubeck-Loebenstien B, Cambier J. Immune senescence. Editorial overview. *Curr Opin Immunol*. 2011; 23: 509–511.
- Aspinall R, Goronzy JJ. Immune senescence. *Curr Opin Immunol*. 2010; 22: 497–499.
- Appay V, Almeida JR, Sauce D, Autran B, Papagno L. Accelerated immune senescence and HIV-1 infection. *Exp Gerontol*. 2007; 42: 432–437.
- Mittler JE, Levin BR, Antia R. T-cell homeostasis, competition, and drift: AIDS as HIV-accelerated senescence of the immune repertoire. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996; 12: 233–248.
- HIV AGING RESEARCH. Telomere/telomerase dynamics within the human immune system: Effect of chronic infection and stress. *Exp Gerontol*. 2011; 46: 135–140.
- Effros RB, Chou JP, Ramirez CM, Wu JE. Telomere/telomerase dynamics within the human immune system: effect of chronic infection and stress. Accelerated aging in HIV/AIDS: novel biomarkers of senescent human CD8+ T cells. *PLoS One*. 2013; 8: e64702.
- Pathai S, Bajillan H, Landay AL. Is HIV a model of accelerated or accentuated aging? *High KPJ Acquir Immune Defic Syndr*. 2014; 69: 833–842.
- High KP, Brennan-Ing M, Clifford DB, Cohen MH, Currier J, Deeks SG, et al. OAR Working Group on HIV and Aging. HIV and aging: state of knowledge and areas of critical need for research. A report to the NIH Office of AIDS Research by the HIV and Aging Working Group. *J Gerontol A Biol Sci Med Sci*. 2012; 60: 1–18.
- Blanco JR, Caro AM, Pérez-Cachafeiro S, Gutiérrez F, Iribarren JA, González-García J, et al. HIV infection and aging. *AIDS Rev*. 2010; 12: 218–230.
- Rickabaugh TM, Jamieson BD. A challenge for the future: aging and HIV infection. *Immunol Res*. 2010; 48: 59–71.

40. Gebo KA, Moore RD. Treatment of HIV infection in the older patient. *Expert Rev. Anti Infect Ther.* 2004; 2: 733-743.
41. Steven G Deeks. HIV Infection, Inflammation, Immunosenescence, and Aging. *Annu Rev Med.* 2011; 62: 141–155.
42. Manzardo C, Zaccarelli M, Agüero F, Antinori A, Miro JM. Optimal timing and best antiretroviral regimen in treatment naïve HIV-infected individuals with advanced disease. *Aquir Immune Defic Syndr.* 2007; 46: 9-18.
43. Casau NC. Perspective on HIV infection and aging: emerging research on the horizon. *Clin Infect Dis.* 2005; 41: 855-863.
44. Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Curr Opin Oncol.* 2007 Sep; 19: 446-451.
45. Nogueras M, Navarro G, Antón E, Sala M, Cervantes M, Amengual M, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis.* 2006; 6: 159.
46. Zhao H, Goetz MB. Complications of HIV infection in an ageing population: challenges in managing older patients on long-term combination antiretroviral therapy. *J Antimicrob Chemother.* 2011; 66: 1210-1214.
47. Gebo KA, Justice A. HIV infection in the elderly. *Curr Infect Dic Rep.* 2009; 11: 246-254.
48. Avelino-Silva VI, Ho YL, Avelino-Silva TJ, Santos Sde S. Aging and HIV infection. *Ageing Res Rev.* 2011; 10: 163-172.
49. Tumbarello M, Rabagliati R, de Gaetano Donati K, Bertagnolio S, Montuori E, Tamburrini E, et al. Older age does not influence CD4 cell recovery in HIV-1 infected patients receiving highly active antiretroviral therapy. *BMC Infect Dis.* 2004; 6: 46.
50. Deeks SG. HIV infection, inflammatory, immunosenescence, and aging. *Annu Rev Med.* 2011; 18: 141-155.
51. Capeau J. Premature aging and premature age-related comorbidities in HIV-infected patients: facts and hypotheses. *Clin Infect Dis.* 2011; 53: 1127-1129.
52. Simone MJ, Appelbaum J. HIV in older adults. *Geriatrics.* 2008; 63: 6-12.
53. Marzolini C, Back D, Weber R, Furrer H, Cavassini M, Calmy A, et al. Swiss HIV Cohort Study Members. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother.* 2011; 66: 2107-2111.
54. Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy.* 2007; 27: 1379-1386.
55. Rhee MS, Greenblatt DJ. Pharmacologic consideration for the use of antiretroviral agents in the elderly. *J Clin Pharmacol.* 2008; 48: 1212-1225.
56. Spaulding A, Rutherford GW, Siegfried N. Stavudine or zidovudine in three-drug combination therapy for initial treatment of HIV infection in antiretroviral-naïve individuals. *Cochrane Database Syst Rev.* 2010; CD008651.
57. Henry K. Internal medicine/primary care reminder: what are the standards of care for HIV-positive patients aged 50 years and older. *HIV/AIDS Rep.* 2009; 6: 153-161.
58. Onen NF, Overton ET, Seyfried W, Stumm ER, Snell M, Mondy K, et al. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. *HIV Clin Trials.* 2010; 11: 100-109.
59. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Res.* 2010; 85: 201-209.
60. Antinori A, Ammassari A, Torti C, Marconi P, Andreoni M, Angarano G, et al. Italian consensus statement on management of HIV-infected individuals with advanced disease naïve to antiretroviral therapy. *Infection.* 2009; 37: 270-282.
61. Manfredi R. HIV infection and advanced age emerging epidemiological, clinical, and management issues. *Ageing Research Reviews.* 2004; 3: 31-54.
62. Kelly A Gebo. Epidemiology of HIV and response to antiretroviral therapy in the middle aged and elderly. *Aging health.* 2008; 4: 615–627.
63. Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. *Rev Endocrinolog.* 2011; 8: 11-21.
64. Mansky KC. Aging, human immunodeficiency virus, and bone health. *Clin Interv Aging.* 2010; 5: 285-292.
65. Boehme RE, Cameron S. Key data from the 11th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV. *Antivir Ther.* 2009; 14: 1195-1208.
66. Tan IL, McArthur JC. HIV-associated neurological disorders: a guide to pharmacotherapy. *CNS Drugs.* 2012; 26: 123-134.
67. Gebo KA. HIV and aging: implications for patient management. *Drugs Aging.* 2006; 23: 897-913.
68. Cordery DV, Cooper DA. Optimal antiretroviral therapy. *Sex Health.* 2011; 8: 534-540.
69. Ghidei L, Simone M, Salow M, Zimmerman KM, Paquin AM, Skarf LM, et al. Aging, Antiretrovirals, and Adherence: A Meta Analysis of Adherence among Older HIV-Infected Individuals. *Drugs & aging.* 2013; 30: 809-819.
70. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med.* 2000; 133: 21–30.
71. Nguyen N, Holodniy M. HIV infection in the elderly. *Clin Interv Aging.* 2008; 3: 453–472.
72. Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JS. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr.* 2004; 35: 261–268.
73. Dunham PJ, Karkula JM. Effects of a pharmacy-care program on adherence and outcomes. *Am J of Pharm Benefits.* 2012; 4: e8–e14.
74. Viswanathan H, Anderson R, Thomas J. Evaluation of an antiretroviral medication attitude scale and relationships between medication attitudes and medication nonadherence. *AIDS Patient Care STDS.* 2005; 19: 306–316.
75. Ruppar TM, Conn VS, Russell CL. Medication adherence interventions for older adults: literature review. *Res Theory Nurs Pract.* 2008; 22: 114–147.
76. Johnson MO, Catz SL, Remien RH, Rotheram-Borus MJ, Morin SF, Charlebois E, et al. Theory-Guided, Empirically Supported Avenues for Intervention on HIV Medication Nonadherence: Findings from the Healthy Living Project. *AIDS Patient Care STDS.* 2003; 17: 645–656.
77. Barclay TR, Hinkin CH, Castellon SA, Mason KI, Reinhard MJ, Marion SD, et al. Age-associated predictors of medication adherence in HIV-positive adults: health beliefs, self-efficacy, and neurocognitive status. *Health Psychol.* 2007; 26: 40–49.
78. Cuzin L, Delpierre C, Gerard Sp, Massip P, Marchou B. Immunologic and Clinical Responses to Highly Active Antiretroviral Therapy in Patients with HIV Infection Aged 150 Years. *Clin Infect Dis.* 2007; 45: 654–657.
79. Sherr L, Harding R, Lampe F, Johnson M, Anderson J, Zetler S, et al. Clinical and behavioural aspects of aging with HIV infection. *Psychol Health Med.* 2009; 14: 273–279.
80. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Swiss HIV Cohort Study. Comorbidity and multimorbidity because of non-AIDS diseases, particularly diabetes mellitus, cardiovascular disease, non-AIDS-defining malignancies, and osteoporosis, become more important in care of HIV-infected persons and increase with older age. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis.* 2011; 53: 1130-1139.
81. Costagliola D. Demographics of HIV and aging. *Curr Opin HIV AIDS.* 2014; 9: 294-301.
82. Roger KS, Mignone J, Kirkland S. Social aspects of HIV/AIDS and aging: a

- thematic review. *Can J Aging*. 2013; 32: 298-306.
83. Branson BM, Handsfield HH, Lampe MA. Vital signs: HIV testing and diagnosis among adults. *MMWR Morb Mortal Wkly Rep*. 2010; 59: 1550-1555.
 84. Nokes KM. Symptom disclosure by older HIV-infected persons. *Assoc. Nurses AIDS Care*. 2011; 22: 186-192.
 85. Vance DE. Aging with HIV: clinical considerations for an emerging population. *Am J Nurs*. 2010; 110: 42-47.
 86. Hirsch AA, Compan A, Lawrence RH, Briggs JM, Yadavalli GK, Fuller MA. Pilot study to assess subjective and objective reporting of potential adverse drug reactions in older versus younger HIV-infected patients using antiretroviral therapy. *J Assoc Nurses AIDS Care*. 2012; 23: 397-408.
 87. Falade-Nwulia O, Thio CL. Liver disease, HIV and aging. *Sex Health*. 2011; 8: 512-520.
 88. Stone VE, Bounds BC, Muse VV, Ferry JA. Case records of the Massachusetts General Hospital. Case 29-2009. An 81-year-old man with weight loss, odynophagia, and failure to thrive. *N Engl J Med*. 2009; 361: 1189-1198.
 89. Peate I. Human immunodeficiency virus and the older person. *Br J Nurs*. 2007; 16: 606-610.
 90. Sankar A, Nevedal A, Neufeld S, Berry R, Luborsky M. What do we know about older adults and HIV? A review of social and behavioral literature. *AIDS Care*. 2011; 23: 1187-1207.
 91. Vance DE, McGuinness T, Musgrove K, Orel NA, Fazeli PL. Successful aging and the epidemiology of HIV. *Clin Interv Aging*. 2011; 6: 181-192.
 92. Rose MA. Planning HIV education programs for older adults: cultural implications. *J Gerontol Nurs*. 2004; 30: 34-39.
 93. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *The Lancet*. 2013; 382: 1525-1533.
 94. Ruiz M, Cefalu C, Ogbuokiri J. A dedicated screening program for geriatric HIV-infected patients integrating HIV and geriatric care. *J Int Assoc Physicians AIDS Care (Chic)*. 2010; 9: 157-161.
 95. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007; 55: 780-791.
 96. Warren MW. Care of the chronic aged sick. *Lancet*. 1946; 1: 841-843.
 97. Matthews DA. Dr. Marjory Warren and the origins of British geriatrics. *J Am Geriatr Soc*. 1984; 32: 253-258.
 98. Deyo R, Applegate WB, Kramer A, Hyer K, Pawlson LG, Winograd CH. Medicare reimbursement for geriatric assessment: report of the American Geriatrics Society Ad Hoc Committee on Geriatrics Assessment. *J Am Geriatr Soc*. 1991; 39: 926-931.
 99. Wieland D, Rubenstein LZ, Hedrick SC, Reuben DB, Buchner DM. Inpatient geriatric evaluation and management units (GEMs) in the veterans health system: diamonds in the rough? *J Gerontol*. 1994; 49: 195-200.
 100. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit: a randomized clinical trial. *N Engl J Med*. 1984; 311: 1664-1670.
 101. Tinetti ME. Clinical practice: preventing falls in elderly persons. *N Engl J Med*. 2003; 348: 42-49.
 102. Wieland D. The effectiveness and costs of comprehensive geriatric assessment and management. *Crit Rev Oncol Hematol*. 2003; 48: 227-237.