ORIGINAL ARTICLE

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Much cheaper, almost as good treatment: a possible approach to guarantee sustainability of HIV care?

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Combination antiretroviral therapy (cART) has been one of the most successful medical intervention in the last part of the past century, turning HIV infection from a lethal disease into a treatable chronic condition, with a life expectancy just slightly reduced compared to general population (1,2). Based on data of the United States, Walensky et al. (3) estimated that in 2003 the survival benefit related to cART was about 160 months, that greatly exceeded the one achieved by treatments for many other chronic diseases, such as chemotherapy for non-small-cell lung cancer, which results in an average survival benefit of 7 months, or bone marrow transplantation for relapsed non-Hodgkins lymphoma which is associated with a survival benefit of 92 months.

cART have also provided good value for money, as shown in a number of cost-effectiveness studies (4), however its widespread adoption in clinical practice, made HIV infection one of the chronic diseases with the highest annual per capita cost of care (5), with antiretroviral (ARV) drugs representing about two-thirds of this cost.

Although the absolute number of patients receiving care for HIV infection in many high-income countries is lower compared to other chronic diseases, HIV infection imposes high costs on the health systems. Furthermore, as people continue to be infected with HIV and people living with HIV (PLHIV) are living longer due to cART, one can expect that in industrialized countries the number of PLHIV, as well as the population costs for HIV treatment and care, will continue to increase in the foreseeable future.

In a province of northern Italy, Magoni et al. observed an average annual increase of 7.0% of the number of patients receiving care for HIV infection over the period 2003-2007 (5), with population costs growing at an annual rate of 13.1%. In Italy, at the national level, the expenses for ARV drugs increased by 75% between 2008 and 2011 (from €377.9 million in 2008,to €661.5 million in 2011; +20.5% on average per year) (6).

Similar figures has been reported for the United Kingdom, where the average annual growth rate of PLHIV using NHS services has been 14.0% over the period 1997-2006 and this rate was estimated to be 6.0% per year over the years 2006-2013 (7). The annual population costs were estimated to increase from £ 104 million in 1997 to £483 million in 2006 (+18.6% per year) and up to £721 million (+5.9% per year) in 2013.

The patients followed in the Southern Alberta Cohort, that includes all diagnosed HIV-infected patients living within Southern Alberta area, Canada, increased by 74% from 526 in 1997/1998 to 920 in 2005/2006 (on average +7.2% per year) (8). Total direct care costs for all HIV-infected patients within the region increased by 69% from 1997/1998 to 2005/2006. To note is the fact that the mean cost per patient per month has not increased significantly since cART introduction in clinical practice and also the distribution among cost components has remained stable over the period studied.

It is also likely that costs will increase further, firstly because of expanding indication for cART initiation. Accumulating evidence suggests in fact that starting treatment earlier in the course of HIV disease may reduce AIDS and non-AIDS associated morbidity and mortality (9,10), and may decrease the risk of sexual transmission of infection with a potential impact on the future course of the epidemic (11). Based

on this evidence several guidelines now recommend offering cART also to patients with a minor level of immunosuppression (12,13) and the strategy of treating all individuals diagnosed with HIV, regardless of CD4 cells count (14) has recently gained momentum.

Secondly, costs may raise as a consequence of the introduction in clinical practice of new and more expensive drugs aimed to naive and experienced subjects. In the same direction will also act the change in the mix of regimens, caused by the shift of treated subjects towards more costly cART combinations as they move through subsequent lines of treatment.

Finally, the management of costly co-morbidities will have an impact on the costs of care. These co-morbidities, are already more frequent among PLHIV relative to the general population (5), and this will be increasingly so in the future, with the ageing process and the cumulative effects of HIV disease on overall health .

In the present period of cutting public expenditure for health, the increasing trends of population costs for HIV treatment and care are raising serious concerns in high-income countries, this issue is even more problematic for middle- and low-income countries (7). Therefore, with the objective of reconciling the appropriateness of therapeutic decisions with economic sustainability, a series of strategies have been proposed, including choice of less expensive drug combinations, innovative drug procurement strategies, use of co-formulated ARVs, monotherapy and use of generic drugs.

The choice of the least expensive between clinically appropriate alternatives has become an accepted practice, in particular for first line cART, for which Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-based regimens, despite lower costs, have shown similar effectiveness compared to Protease Inhibitor/ritonavir boosted (PI/r)-based (15).

For exploiting the opportunities offered to the procurement process for ARV drugs by standardized therapeutic decisions, the approach of therapeutic tender has been proposed by London NHS Trusts. This approach is aimed to promote an agreement among care providers on a limited number of drug choices, among those in line with published British and international guidelines, in order to stimulate volume growth and significantly reduce acquisition costs while protecting the access to and the quality of clinical care for all PLHIV (16).

Regimens co-formulated in a single tablet (STR) represent a strategy that may associate a reduction in pill burden, and consequently potential improvements in adherence to treatment, with cost savings. In an observational study from the United Kingdom, Beck et al found that STR was as effective as the two- and three-pill regimens of the same drugs, in terms of suppressing viral replication (17). These authors also estimated that use of a single pill as a first line regimen would determine a 20% savings on healthcare costs at six and 17% of costs at twelve months compared with the use of Tenofovir/Emtracitabine plus Efavirenz that generated the next lowest costs.

PI/r-based monotherapy has been proposed as one of the most promising treatment simplification strategies, in terms both of clinical effectiveness and costs (18,19). At the moment uncertainties exist about the number of patients that could be eligible for such strategies and consequently on their financial impact. Gazzard et al. (20) assumed that 40% of patients currently treated in the United Kingdom (about 18,000 individuals) would be eligible for the switch to monotherapy, with the potential to save up to £ 60 million per year. Earlier studies suggested that, although a population of patients treated with monotherapy may experience an overall net increase in quality-adjusted survival, compared with recipients of the standard cART, some individuals could experience a suboptimal outcome (19). More recently, a meta-analysis of published trials (21) shows that patients that switch from cART to PI/r monotherapy A have a slightly, but significantly lower chance to maintain viral suppression, although patients who experience a virological rebound while on monotherapy A have a very high chance of achieving again viral suppression following resumption of a multidrug regimen. These observations highlight a very relevant ethical issue that may arise in relation to cost savings interventions, and that reflect the potential tension between population benefits and the preferences and outcomes at the individual level. Can we accept a decrease, although apparently limited, of clinical effectiveness in order to obtain a decrease in health care costs?

The results of a recent modelling exercise on the use of generic antiretroviral drugs further exemplifies this issue. Walensky et .al (22) estimated that the switch to a 3 pill cART regimen of generic efavirenz, generic lamivudine, and branded tenofovir would result in the USA in a yearly saving of $6,100 per patient, amounting at population level to yearly saving of nearly $1 billion (the overall market for antiretroviral drugs was estimated at nearly $9 billion in the USA in 2011). The authors estimated for each individual patient switched from first line branded to generic-based cART, a lifetime average cost saving of $42,500, but also an average loss of quality-adjusted survival of 0.37 years.

Economic evaluation in the context of health care is usually applied to new interventions that are considered to be more effective and are certainly more costly than those currently in use. In the most widely used analysis models, the aim is to estimate the incremental cost effectiveness ratio (ICER) i.e. the addi-

tional monetary cost that we have to pay to obtain an additional heath benefit. ICER is usually expressed as money per quality adjusted year of life (QUALY) gained, and an intervention showing an ICER below 30,000 €per QUALY gained has been generally considered as acceptable under the economic point of view in most industrialized countries.

The interpretation of the results of the paper by Walensky et al may, to some extent, need to turn upside down the usual perspective of economic evaluation in health. In fact this paper it is possible to estimate a saving of $114,800/QALY lost, and this ratio, using the terminology originally proposed by Kent and colleagues (23), can be defined as "decremental cost effectiveness ratio" (DCER). However, there is no consensus on the acceptability threshold for a DCER, and even, we would argue, if a decrementally effective intervention could be seen as acceptable at all.

Examples of implementation of decrementally cost effective interventions exist also in the field of HIV . When it was devised, use of nevirapine for prevention of mother-to-child transmission of HIV could have been considered as a suboptimal intervention. Nonetheless it has been wide adopted in less developed countries . Few studies have until now formally analyzed the issue of decremental cost effectiveness. In an analysis of 2128 cost- effectiveness ratios in 887 papers published between 2002 and 2007 only 9(0.4%) addressed interventions that appeared decrementally cost-effective (24).

Kent and colleagues, however, have argued that the threshold for acceptability should be substantially higher for DCER than that used for ICER (23). These authors quote David Hume who in 1740 wrote that individuals place more value on loss than they do on equivalent gain. The general attitude does not seem to have changed in this regard in after almost three centuries . O' Brien et al (25) reviewed a series of studies related to health matters and they found that the "willingness to accept", the compensation requested for giving away something that is already obtained, is 2 to six times greater than the " willingness to pay" for something we do not have yet.

A crucial problem to be addressed is the potential clinical risk associated with "suboptimal" care. For example, the potentially increased risk of viral failure associated with monotherapy could be acceptable if the rapid viral suppression obtained after resuming cART implies negligible health risks in the long term.

And finally, the use of any saving in the health care expenditure must be discussed. For example, as suggested by Walensky et al, use of generic ARVs could be more acceptable caregivers and patients' advocates if the saving were used to finance other needs in the field of HIV care (22).

In the foreseeable future funding for adoption of new interventions or expansion of access to care will increasingly depend on reallocation of existing resources rather than on availability of new resources. Decision about this process need the active involvement of all interested stakeholders, in the first place the patients, the medical community and also the drug industry.

References

1. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293-9.
2. Antiretroviral Therapy Cohort Collaboration, Zwahlen M, Harris R, May M, Hogg R, Costagliola D, et al. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. Int J Epidemiol. 2009;38:1624-33.
3. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, Weinstein MC, Freedberg KA. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006 ; 194:11-9.
4. Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seage GR, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. N Engl J Med. 2001;344:824-31.
5. Magoni M, Scarcella C, Vassallo F, Lonati F, Carosi G, Castelnuovo F, Quiros-Roldan E, Albini L, Gennaro N, Bishai D, Tramarin A, Torti C. The evolving burden of HIV infection compared with other chronic diseases in northern Italy. HIV Med 2011;12:129-37.
6. Gruppo di lavoro OsMed. L'uso dei farmaci in Italia. Rapporto nazionale anni 2008-2011.
7. Mandalia S, Mandalia R, Lo G, Chadborn T, Sharott P, Youle M, et al. Rising population cost for treating people living with HIV in the UK, 1997-2013. PLoS One. 2010; 5(12):e15677.
8. Krentz HB, Gill MJ. Cost of medical care for HIV-infected patients within a regional population from 1997 to 2006. HIV Med. 2008;9:721-30.
9. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009;360:1815-26.
10. Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet 2009;373:1352-63.
11. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493-505.
12. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 rec-

ommendations of the International Antiviral Society-USA panel. JAMA 2012 ;308:387-402.

13. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/ adultandadolescentgl.pdf. Section accessed [March 1, 2013].
14. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 2009; 373:48–57.
15. Beck EJ, Mandalia S, Lo G, Sharott P, Youle M, Anderson J, et al. Cost-effectiveness of early treatment with first-line NNRTI-based HAART regimens in the UK, 1996-2006. PLoS One. 2011;6(5):e20200.
16. Foreman C, Gazzard B, Johnson M, Sharott P, Collins S. Maintaining cost-effective access to antiretroviral drug therapy through a collaborative approach to drug procurement, consensus treatment guidelines and regular audit: the experience of London HIV commissioners and providers. Sex Transm Infect. 2012;88:112-5.
17. Beck EJ, Mandalia S, Sangha R, Youle M, Brettle R, Gompels M, et al. Lower Healthcare Costs Associated with the Use of a Single-Pill ARV Regimen in the UK, 2004-2008. PLoS One. 2012;7(10):e47376. Epub 2012 Oct 30.
18. McKinnon JE, Mellors JW, Swindells S. Simplification strategies to reduce antiretroviral drug exposure: progress and prospects. Antivir Ther. 2009;14:1-12.
19. Schackman BR, Scott CA, Sax PE, Losina E, Wilkin TJ, McKinnon JE, et al. Potential risks and benefits of HIV treatment simplification: a simulation model of a proposed clinical trial. Clin Infect Dis 2007; 45:1062-70.
20. Gazzard B, Hill A, Anceau A. Cost-efficacy analysis of the MONET trial using UK antiretroviral drug prices. Appl Health Econ Health Policy. 2011;9:217-23.
21. Mathis S, Khanlari B, Pulido F, Schechter M, Negredo E, Nelson M, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. PLoS One. 2011;6(7):e22003.
22. Walensky RP, Sax PE, Nakamura YM, Weinstein MC, Pei PP, Freedberg KA, Paltiel AD, Schackman BR. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. Ann Intern Med 2013;158:84-92.
23. Kent DM, Fendrick AM, Langa KM. New and dis-improved: on the evaluation and use of less effective, less expensive medical interventions. Med Decis Making 2004;24:281-6.
24. Nelson AL, Cohen JT, Greenberg D, Kent DM. Much cheaper, almost as good: decrementally cost-effective medical innovation. Ann Intern Med 2009;151:662-7.
25. O'Brien BJ, Gertsen K, Willan AR, Faulkner LA. Is there a kink in consumers' threshold value for cost-effectiveness in health care? Health Econ. 2002 Mar;11(2):175-80.