

HCV: Will Drug Users Benefit of the Direct Acting Antivirals?

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Direct acting antivirals (DAA) drastically transform the prognosis of chronic HCV infections, giving, for the first time, in the absence of a vaccine [1, 2], the opportunity of curing almost every infected person. Their prices are, however, so high that, in most countries few patients are able to pay for them. In countries where treatments are financed through a welfare system, their prescription is restricted to patients likely to progress towards a primitive cancer of the liver or a terminal hepatic insufficiency. For now and until the expiration of the current patents (2026 for simeprevir), this rule will exclude 70% of infected people and, for the remaining 30% with active diseases, may postpone its prescription 10 years after the contamination when the infection occurred at an early age [3-5].

For three years, an unusually high number of articles have dealt with the cost-effectiveness of these treatments. Most conclusions were positive with some restrictions concerning the genotype 2 and 3 related to their good response to pegylated interferon-ribavirin [6-9]. Usually the upper limit considered acceptable is of the order of \$, CH or €100,000/QALY but estimations have been as low as \$15709/QALY for treating all patients [10]. However, real life costs may be much higher than initially believed [11], underlining the influence (variability) of initial hypotheses on the final result. Without stressing the lack of a sufficient description of frequent conflicts of interest associated with these publications (subject already treated by Saab et al. [12]), we can emphasize that if the possible impact of this cost on access to treatment may be discussed, the appropriateness of its calculation is almost seldom discussed. They only rephrase the "ethical" proposal accepted for highly active antiretroviral treatments of AIDS in low income countries where their prohibitive costs are offset by allowing a generic production.

Yet this assumption is worth investigating. One needs to understand how such exorbitant prices may be accepted, unconnected to the expenditures related to the development of the molecules [13, 14]: A price is indexed on the "added value" of a treatment which is the reduction in the cost of the care of a patient treated by a new compound compared to an absence of treatment or to the cost of an existing treatment. The cost of monitoring the disease, of management of decompensation and of primary liver cancer and transplantation, is weighted by the average cost of a quality of life index linked to the disease (QALY, HRQOL). It is condensed in the price of a treatment which, unlike HIV, is not lifelong, but has only a duration of three months. Of course, this estimation covers also the development of the drugs, including the huge international randomized studies that "concern" a small subgroup of medical specialists in the whole

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world. This method has the advantage, for the industry, to be able to calculate in advance the expected benefits of a new drug, to justify its price with the government that will grant them the marketing prices and define their development strategies and, for the government, to have "rational" arguments to justify the authorizations. But this reasoning has to be criticized:

- As long as the added value was low, this approach seemed acceptable, even if the proposed prices were high. The development of DAA, able to cure HCV hepatitis, has shown that it was obviously inappropriate. At present prices a limited number of patients have access to HCV treatment. No one would be able to pay the resulting suggested prices for drugs capable of curing AIDS or diabetes. It suggests that the previous estimations of the incremental cost-effectiveness ratios may have been too favourable to the pharmaceutical companies. Its reappraisal could lead to a reduction of the expected tripling of the healthcare expenditure in the next fifty years.
- The savings estimated for society through the decrease in HCV morbidity and mortality are restricted to a disease, assuming that this saving would not be balanced by the occurrence of other diseases. This assumption is false. Since most people are not healthy when they die, other cares will need to be funded when their hepatitis C are cured: Patients with an alcohol/HCV related liver disease may die of a liver cancer despite the cure of their HCV infection [13] and a person developing lung cancer after the healing of his hepatitis C (which is not uncommon considering the consumption of tobacco and cannabis by drug users) may receive a treatment

which can cost more than the treatment of the hepatitis and should be added to the social cost of his HCV care. Of course, an accurate predicting is impossible given the contingency of these developments. It may be the main reason of this willful blindness beside the evident conflicts of interest of the involved decision makers. If the societal cost is to be included, then obviously, the issue is more complex than a simple equation. Thus, none of these cost-effectiveness estimations are relevant when the global economy is considered. What will be requested for the social return on investment? Since most of the newly infected patients have other problems than healthcare such as housing, work (when they are not illegal migrants) and, if they survive, pensions, they will not be able to pay back their full cost.

- New infections are mainly related to an epidemic among intravenous drug users. Compared to the test and treat initiative proposed and implemented for HIV [15], it is obvious that the strategy restricting treatment prescriptions to the advanced diseases will have a limited impact on the incidence of the new contaminations and on the course of the epidemic.
- National recommendations are unanimous in proposing a systematic HCV screening of populations at risk including drug users. The separation, sometimes for years, between the hepatitis diagnosis and its treatment will have a negative impact on the QALY of every HCV carrier. The incentive to be screened is unlikely to be heard by symptomless drug users, renowned for their "discounting". It can be dissuasive and may slow down, if not prevent, the control of the epidemic.

Economic theories consider that the market's law manages to set the fair price of a commodity. It is not true for medicinal products:

- In a pure liberal system, it is clear that the population of the patients infected by HCV would be, in its vast majority, unable to pay the price which is asked for the AAD. This extra cost has only been covered through solidarity in high income countries. In the United States, 70% of these treatments are financed by Medicaid [8] and, in France, 100% by Social Security. For now, the cost of treatment is not a significant political or medical issue, but the amounts achieved give them a visibility which could lead to a questioning of societal solidarity. Would a majority of US citizens agree to pay the \$136 billion needed to heal every infected patient, 61 billion of which would be paid by the government [8]? The crisis and the recent rise of extremism give cause to doubt its acceptance by the electorate.
- Many molecules are the subject of initial applications for marketing authorization in the US. The registration procedure is often faster than in other developed countries, but this preference may have other motivations. The obligation to accept, without negotiation, the prices offered by pharmaceutical companies for Medicaid [16] besides the financing of political campaigns, may be one of their incentives. Accepting a high price for a blockbuster advantages the country that hosts the laboratory that produces the medication. Taxes on foreign profits generated by the molecule may more than compensate the expenditure of treating its population. For thirty years, the creativity of the British pharmaceutical industry has made the UK a pioneer in this field. Starting from astronomical prices, any later rebate, even

small, can be presented as a success of the price bargaining. Thus, the proposed annual cost of a new treatment used for melanomas can reach \$250, 000. Of course, countries with no or less creative pharmaceutical industry are systematically penalized.

- Competition, opened by putting on the marketplace, in a very short period, molecules with similar efficiencies, does not play thoroughly because prices are aligned with those of the first drug to be put on the market. If hospitals in France and, organizations such as the Veterans Health Administration in the US, are entitled to create competition between these treatments guaranteeing preferential prescription of the "best bidder", States do not use-and may even be prohibited-to use this procedure. France, for example, has the obligation to offer a price lying within the range of prices offered by its neighbours.
- The added value of new treatments has been calculated on the basis of healthcare costs in the wealthiest countries where it is a significant part of their GDP. But this conclusion is not universal. Applying the same premises to Spain, where the cost-effectiveness threshold of new HCV treatments was €40000/QALY, DAA were not found cost-effective [17]. In lower income countries like sub-Saharan Africa, this threshold would be much lower. But these estimations are never proposed, underlining the internalization by the authors of an impossible access to these treatments for low income countries.

Prices of medicinal products do not follow the laws of a free market: For instance, considering that current laptop have the same power as mainframes thirty years ago, no one would accept today a 10% discount on the original marketing price as a fair deal. For medicinal products, a change of perspective is needed. Since the cost of DAA treatment are paid by states, they could have other ambitions than to only consider the limited project of decreasing the number of deaths. They should consider the impact of these prices on society: In the US, the price of one year of life for a cancer patient reached \$207 000 in 2013, an increase of 10% per year since 1995 [18]. The efficacy of the DAA allows the planning of HCV eradication through a universal "test and treat" approach following the model of HIV. This option is not currently conceivable even in high income countries. An accurate evaluation of the number of DUs who are infected and of the willingness of the different states to eradicate the HCV epidemic could lead to an estimation of the amount each country would accept to pay. Then pharmaceutical companies would have to compete so that treatment of first intention would be awarded to the lowest bidder. This "liberal" approach would be more socially acceptable than the current solution. The 99% discount obtained by Egypt for sofosbuvir as soon as 2013 demonstrates that governments, when they have the will, may negotiate affordable deals [12].

In conclusion, estimations that justify today the amount charged by pharmaceutical companies seem unfounded. The proposed strategies, to treat only the most severe patients, ensure a regular renewal of infections due to the maintenance of endemic hepatitis C and, ultimately, an increase in the overall cost of this disease, while a "universal" treatment, as proposed for HIV could have a much faster impact especially as treated patients would

be cured which is not the case for HIV [19,20]. Caregivers accept current guidelines because they fit a traditional representation of health care organizations treating individual patients. They ignore the modern vision of a cost/effective population health strategy that, unfortunately, remains outside the health professionals concern and the scope of politics. Common ground should be found, leaving the pharmaceutical industry, one of the most

profitable industries, sufficient room for profits and to continue to innovate while remaining consistent with public health goals of nations that fund them. Monetary incentives for screening and treating drug users, allowed by the lower price of the drugs, could then be proposed. Their efficiency has been shown to improve screening [21-23] and compliance among drug users [24-26].

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