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Innovation and Standards in Clinical Practice: the Case of HIV Treatments

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Innovation and Standards in Clinical Practice: The Case of HIV Treatments

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Abstract

The goal of this study was to analyze the emergence of treatment standards associated with the adoption of anti-HIV drug innovations in the empirical setting of Italian clinical practice. Due to the rapid pace of technological change and the initial uncertainty concerning capabilities and indications of new treatments, the emergence of standard patterns of care turned out to be far from predictable and straightforward. Health providers' links to an international medicine and their internal coordination mechanisms were found to be associated with clinical decisions. Effectiveness and health costs of diverging treatment strategies were also compared.

1. Introduction

Starting from the mid-1990s, the introduction of new powerful drug combinations called HAART (Highly Active Antiretroviral Therapy) has revolutionized HIV/AIDS care. HAART has radically changed the natural course of HIV infection (Palella et al., 1998), which is rapidly becoming a chronic manageable disease. The range of therapeutic alternatives has widened over the years and clinical treatment models have been developing as temporal sequences of interdependent combination therapies.

The objective of this study is to investigate the emergence of different treatment patterns after the introduction of HAART in the setting of Italian clinical practice. Namely, three research issues are addressed. First, we describe the evolution of individual therapeutic paths and the emergence of typical treatment patterns in the HAART era. Second, we analyze whether structural and organizational characteristics of health providers are related to therapeutic choices. Finally, we compare the effectiveness and the efficiency of alternative treatment patterns.

The empirical work is based on detailed evidence at the patient-level and on original data from a large national survey of HIV/AIDS care providers.

This paper contributes to the literature on medical innovations in several ways. It carefully describes the development and nature of treatment standards in which a technological innovation

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becomes embedded and through which it spreads. To better observe the pace and degree of standardization, it focuses on whole individual therapeutic histories instead of single drug treatments and, in doing so, it introduces sequence analysis methodology for the study of treatment patterns.

The article proceeds as follows. In Section 2 we introduce the theoretical background on adoption of medical innovations and standard setting in clinical practice, and we describe the recent evolution of HIV/AIDS care. Section 3 illustrates patient and provider data, whereas the methodology adopted in the empirical analysis is explained in Section 4. Study findings are presented and discussed in Section 5. Section 6 reports some concluding remarks.

2. Innovation and treatment standards in HIV care

2.1. Innovation dynamics in HIV treatments

Classical diffusion theory assumes that innovations are sufficiently well defined for individuals to be able to assess their relative advantage, risk, and cost (Geroski, 2000). Actually, as Rogers (1995) points out, all innovations carry some degree of uncertainty for the individual, who is typically unsure of their results and thus feels a need for social reinforcement in order to adopt them. In the case of medical technologies, agreement on capabilities and indications sometimes lags well behind the introduction of innovations, which often occurs when the new products or procedures are not yet completely formed. Many medical technologies develop as they diffuse, in a dynamic manner, with a resulting diffusion pattern different than the classical one, i.e., slower and less predictable (Greer, 1981).

Following the approval of Zidovudine (AZT) for commercial use in the treatment of HIV/AIDS in 1987, new antiretroviral agents have been introduced at an increasingly rapid pace. During the 1990s, a robust correlation between long-run clinical benefits and short-run changes in surrogate endpoints (CD4+ lymphocytes cell count and plasma viral load) was recognized in the scientific literature (Shi et al., 1996). Since the mid-1990s, when routine viral load testing became available, surrogate markers have been easily observable and it has been possible to collect data on new drugs' efficacy without waiting several years for the clinical outcomes to occur. In turn, this has made possible the accelerated approval for new drugs based on such evidence, which, together with widespread compassionate use programs, implied that initial adoption of innovations could occur widely soon after Phase I clinical trials and before much efficacy data were gathered (Maguire, 2002).

Until 1995, other agents belonging to the same pharmacological class of AZT (NRTIs, Nucleoside Reverse Transcriptase Inhibitors) were registered; as from 1996, medications of other pharmacological classes (PIs, Protease Inhibitors; NtRTIs, Nucleotide Reverse Transcriptase Inhibitors; NNRTIs, Non-Nucleoside Reverse Transcriptase Inhibitors) have been commercialized. New powerful combination therapies using at least three antiretroviral agents were introduced and referred to as Highly Active Antiretroviral Therapy (HAART). These advances have been accompanied by the development of more sophisticated diagnostic procedures to assess viral load and HIV mutations (more sensitive plasma HIV-RNA level assays, phenotypic and genotypic assays), useful in supporting clinicians' decisions about therapy administration (Christopherson et al., 1998; Torre and Tambini, 2002).

Due to the rapid changes in HIV treatments and the initial uncertainty concerning their long-term use, possible side effects, and effectiveness outside of controlled trials in a real world setting, in clinical practice HAART adoption may have proceeded in a less straightforward manner than expected from its clear superiority with respect to mono and dual therapies.

2.2. Scientific knowledge and learning-by-doing in the medical profession

Medical doctors have recently been described as a typical example of a people-centered profession, which strongly relies on learning-by-doing as well as on scientific knowledge in everyday practice (Foray and Hargreaves, 2003). Physicians build up their expertise through a combination of scientific, explicit knowledge and learning-by-doing experience from their work with patients.

The failure of researchers to report consistent findings and to include clinically important details diminishes the role of scientific literature in resolving the uncertainty surrounding new health technologies. In a study analyzing the receipt and use of medical information by practicing physicians in local community hospitals, Greer (1988) finds that local professional communities, in spite of their links to an international medicine, are rather closed systems. Most clinicians like to see a general trend before they adopt a new technology, and the general trend is often the local trend. Local consensus is achieved through a process of personal communication regarding risk, benefit and appropriateness; opinion leaders are important actors in this assessment.

The efficacy of triple combination therapy and its superiority with respect to mono and dual therapies were first assessed in randomized clinical trials, whose findings were quickly reported in a number of specialized academic and technical journals (Hammer et al., 1997; Montaner et al., 1998). Thereafter, it has been explored in numerous multi-center observational studies, with the intent to analyze different features of alternative antiretroviral regimens in clinical daily practice (Mocroft et al., 2003; Palella et al., 1998). Due to multi-center cohort studies, clinical advancements spread and inform therapeutic decisions among practitioners in a large number of even small treatment providers (wards/clinics).

In addition to performing clinical research, physicians may get medical information from meetings, workshops and conferences that periodically take place on the subject. These events are usually sponsored by pharmaceutical companies, which also play a direct role in communicating research findings while marketing their products to doctors. As an aside, it is to be noticed that in Italy physicians treating HIV-positive patients cannot be general practitioners: antiretroviral drugs may be prescribed only by specialized virologists, working in hospital infectious diseases wards/clinics and forming a relatively small and connected community.

Still, we foresee the idiosyncratic component of physicians' treatment choices in HIV/AIDS care to be relevant and lead to high heterogeneity in patient therapeutic patterns. In this setting, we try to assess whether specific structural and behavioral features of the health providers (that is, the clinical centers) may affect treatment decisions, with particular regard to the influences of their links to the international science and internal coordination mechanisms.

2.3. Characteristics and role of standardization in clinical practice

Throughout its professional history, the medical community has developed standardization based on procedures, rules and routines as a powerful tool not only to coordinate the activities of its members, but also to cope effectively with the intrinsic uncertainty of clinical practice. Such behavioral standards can assist in coordination by helping to align expectations, and can reduce measurement and monitoring costs by providing a benchmark against which quality of performance can be judged (David, 1987).

Medical professionals can actually be thought of as information-processing systems that must apply a large repertoire of routines to fit widely varying concrete circumstances (Stinchombe, 1990). Given significant task uncertainty, the particular concrete application of the routines requires individual professional judgment (Langlois and Savage, 2001). Since rigid standardization of productive routines would be ineffective in health care, along with the standardization of professional education, treatment guidelines have been developing over time as a general and flexible system of standards, generally accepted among medical practitioners.

Medical guidelines are systematically revised statements which help physicians select the most appropriate interventions in given circumstances, informing providers on optimal diagnostic, therapeutic and resource management strategies. Typically issued by national and/or international organizations and professional societies widely legitimized by the medical community, guidelines reduce uncertainty in clinical procedures and are generally believed to lead to an overall improvement of health practices (Andrews and Redmond, 2004). They must be developed and constantly updated through a multidisciplinary process that can also involve patients' representatives together with medical doctors, other health professionals and health service managers (Leape, 1990).

With the advent of HAART, treatment guidelines have been developed and continuously revised by international and national scientific boards and expert panels as reference standards of good clinical practice (U.S. Department of Health and Human Services, 1998-2005; British HIV Association, 2001-2005; Commissione nazionale AIDS, 2001-2003). These guidelines now address all major issues arising in therapy administration - such as treatment goals, initiation and discontinuation of therapy, recommended combinations and possible complications, patient adherence - summarizing the state of the art in HIV treatment.

International therapeutic guidelines act as a driving force toward standardization of clinical practice in HIV/AIDS care. Nevertheless, their necessary flexibility and lack of enforcement power leave room for largely discretional treatment decisions. We wish to investigate whether, on the one hand, given the uncertainty that informs all medical culture, this form of standardization can be shown to be effective in terms of health benefits and whether, on the other hand, it implies a loss of efficiency in health services management.

3. Data

3.1. Patient and provider data

ICONA (Italian Cohort Naive Antiretrovirals) is an observational study that recruits HIV-infected adults naive to antiretroviral therapy. Prospective routine data collection in ICONA includes clinical and epidemiological parameters, antiretroviral drug regimens, prophylaxis and

treatment of opportunistic infections, inpatient episodes and death. A previous work evaluated retrospectively health costs incurred by the Italian National Health Service (SSN) for hospital admissions, drugs and major laboratory exams (Merito et al., 2005).

The present study was conducted on 2 983 patients of the ICONA cohort, enrolled between February 1997 and December 2002 in 55 Italian Infectious Diseases Clinics and subsequently starting at least one antiretroviral regimen. Although patients entered the cohort during the whole observation period, there were two major rounds of enrolments, the first running from May, 1997 to the first months of 1998, and the second in 2000, intended to replace the dropouts.

At the beginning of year 2001 a prevalence study (StuPre), relative to the year 2000, collected several data on 168 Italian infectious diseases units providing health services to HIV-infected patients. The StuPre survey gathered information on some structural characteristics of the clinics/wards interviewed, as well as on their inpatient and outpatient activities. Among the clinics surveyed 55 were also participating in the ICONA project, with no geographical or dimensional bias with respect to the entire ICONA population. The North of the Country and some big cities (Rome, Milan) were overrepresented in both studies, reflecting the epidemiology of HIV/AIDS in Italy and the availability of specialized health care services. Providers were all operating within public hospitals, since there is no private sector for the treatment of HIV/AIDS patients in Italy. Main characteristics of providers included in the ICONA project are summarized in Table 1.

Hospital size ranged from 22 to 2 400 beds, with the majority having more than 600 beds. Infectious diseases clinics might offer only ambulatory services (thus having no ward beds) or operate quite large inpatient facilities (up to 60 inpatient beds). In 2000, genotypic resistance testing assays were still performed in few laboratories; there did not seem to be any correlation between the availability of this kind of test (an advanced diagnostic procedure to assess HIV mutations) and the provider size. All the clinics were at least mentioned in some publications as members of a study group and, indeed, all were participating in at least two multi-center studies.

3.2. Individual therapeutic sequences

Based on the frequency of each anti-HIV regimen in our population, characterized by the number and class of molecules in the mix, thirteen common pharmacological combinations and one residual were selected. Individual therapeutic paths were then obtained for all patients in the study, considering the successive antiretroviral therapies, as previously classified, followed by each subject from enrolment to death/drop/administrative censoring. A therapy is modified whenever one or more drugs are abandoned, added, or substituted. The switch may lead to the adoption of a different treatment regimen, or a combination of the same type as the previous one. We identified 619 different therapeutic sequences, including up to 13 switches; most patients (75.1%) experienced not more than 5 therapy changes.

A therapeutic switch may have several clinical meanings. Reasons for discontinuing an antiretroviral regimen that emerge from the ICONA database range from therapy failure to simple therapy updates. More specifically, a drug combination may for instance be changed due to clinical, immunological or virological failure, intolerance to drugs and possible side effects, development of cross resistances among drugs belonging to the same therapeutic class. But we can also find new regimen formulations, without any evidence of failure of the preceding one, and therapy simplifications after successful first line regimens.

Table 1 Providers' structural and operational characteristics.

		N	%	Cum
Hospital beds				
	<=200	10	18.18	18.18
	200-600	13	23.64	41.82
	600-1 000	10	18.18	60.00
	1 000-1 600	10	18.18	78.18
	>1 600	5	9.09	87.27
	N.A.	7	12.73	100.00
Ward beds				
	<=15	14	25.45	25.45
	15-25	17	30.91	56.36
	25-35	17	30.91	87.27
	>35	7	12.73	100.00
Genotypic assays				
	In the center's lab	8	14.55	14.55
	In the hospital's lab	8	14.55	29.09
	In another hospital	17	30.91	60.00
	Not performed	19	34.55	94.55
	Other	3	5.45	100.00
Phenotypic assays				
	In the center's lab	29	52.73	52.73
	In the hospital's lab	7	12.73	65.45
	In another hospital	7	12.73	78.18
	Not performed	8	14.55	92.73
	Other	4	7.27	100.00
Publications (national and international)				
	<=10	20	36.36	36.36
	10-15	14	25.45	61.82
	>15	13	23.64	85.45
	N.A.	8	14.55	100.00
Participation in multi-center studies				
	<=5	8	14.55	14.55
	5-10	17	30.91	45.45
	10-15	13	23.64	69.09
	>15	9	16.36	85.45
	N.A.	8	14.55	100.00
		Mean	(Std.Dev.)	Median
Incidence of HIV inpatient episodes		0.320	(0.307)	0.280
Day Hospital utilization rate		0.345	(0.299)	0.295

For our purposes, a therapeutic sequence is the crucial unit of analysis, since it allows us to summarize the entire patient treatment history and to track the complex interactions between technological advances, clinical decision making and individual response to therapy.

4. Methods

4.1. Sequence analysis

Individual therapeutic paths were subjected to optimal alignment so as to generate interval-level measures of resemblance between pairs of sequences. The inter-sequence distances resulting from this whole sequence analysis methodology were then input to clustering in order to uncover common patterns among treatment sequences.

Optimal alignment (coupled with a standard categorization method) was an appropriate analytical technique in this case. Due to the strong heterogeneity of therapeutic sequences in our database we needed to categorize past treatment histories, trying to detect some common patterns, if any. Moreover, the variable of interest - combination therapies - is categorical, but the process is not Markovian (and maybe not stationary either): at every point in time clinical decisions on what next depends crucially on the entire therapeutic history of a subject.

Optimal alignment measures the edit distance between pairs of sequences, that is, the minimum number of edit operations (insertion, deletion, substitution) on the individual characters of the two sequences required to transform one string into the other (Sankoff and Kruskal, 1983). Clearly the length of the sequences influences the number of transformations required. And in a shorter sequence one substitution is more important than in a longer one. We adopted the strategy of standardizing the edit distance by dividing the transformation distance by the length of the longer sequence.

In our computations we allowed an arbitrary weight or cost to be associated with every edit operation and implemented the Needleman-Wunsch algorithm (the basic algorithm for sequence comparison in the dynamic programming framework that allows for the use of arbitrary weights). The weighted edit distance problem becomes that of finding an edit alignment that transforms one string into the other with the minimum total cost. We chose a uniform insertion/deletion (indel) cost, making insertion and deletion cost the same in all cases, whereas we tried different weighting schemes for substitution costs: simple edit distance, where all editing operations cost one, was compared with two distance measures derived from structured matrices of substitution costs, based either on transition frequencies in the whole ICONA population between the codified drug combinations, or on clinical appraisal of inter-therapy similarities. Although different substitution cost schemes lead to different sequence distances, experimental work (Forrest and Abbott, 1990) indicates that the calculated distances are not substantially affected by even fairly strong perturbations in the substitution costs. We also chose to scale indel costs with respect to substitution costs, trying different parameter values, as a refinement of the alignment distance.

To uncover actual types of patterns in our therapeutic sequences we employed different clustering methods. As is well known, different algorithms for cluster analysis produce slightly different solutions. In the present work we used both various agglomerative hierarchical methods (single linkage, complete linkage, average linkage and Ward linkage), comparing their relative

performance, and a particular partitioning method, the k-medoid algorithm (Kaufman, and Rousseeuw, 1990).

4.2. Regression analysis

To study the impact of various patient and provider characteristics affecting individual treatment histories together with technological development, a multinomial logit model was estimated for the main therapeutic patterns emerging from the clustering of individual sequences. The choice of a multinomial logit specification in our case was justified by two orders of considerations: firstly, the outcome variable was categorical and clearly unordered; secondly, we didn't have any choice specific attribute (actually, in this case of complex treatment histories it is quite simply difficult to figure them out).

Due to the high heterogeneity of individual sequences, together with a reference path, we could clearly identify two comparison patterns of some importance, leaving all other idiosyncratic histories, dispersed over a variety of different pathways, in a residual category. The relevance of the outcome categories we chose to disentangle was defined both in terms of their frequencies in the dataset and the competing standards they represented, given the constraint of limiting the overall number of choices to few alternatives (indeed, the number of parameters in the multinomial logit proliferates with the number of choices requiring large sample sizes).

We compared AIDS-free survival and costs among the identified therapeutic pathways. A Cox proportional hazards model was estimated to assess the effect on AIDS-free survival of the selected treatment histories, once controlled for main confounding factors at baseline. We compared treatment costs associated with the therapeutic pathway categories using multivariate linear regression.

We took account of the enrolment period in which each patient entered the cohort as an indicator of the advancements that had occurred in HAART technology over time. The other explanatory variables included in the regression analyses were drawn from both patient and provider characteristics. Among the former set of covariates there were the following attributes:

demographic characteristics: gender and age at enrolment;

clinical and immuno-virological parameters: CDC stage (clinical stage as classified by the US Centers for Disease Control and Prevention), CD4 T-lymphocyte cells count and plasma viral load (main predictors of prognosis) at baseline, hepatitis C coinfection;

follow-up information: inpatient admissions, new AIDS Defining Events occurred after starting therapy, viral load tests resulting in detectable viremia after therapy initiation (which signal for virological failures of therapies, or at least blips, intermittent episodes of high level viremia); and

behavioral attributes: HIV exposure category.

The latter group of covariates included:

structural characteristics: provider size measured by the number of ward beds, how much specialized on HIV care the provider is, as indicated by the number of HIV+ subjects out of all patients admitted to the ward/clinic, and internal availability of advanced diagnostic procedures (genotypic assessment); and

behavioral attributes: number of national and international publications either as authors or as research group participants, and participation in national and international multi-center clinical studies – which both stand for the amount of research activity going on in the ward/clinic and

proxies for clinicians knowledge updating (publication activity asking for more active involvement) – as well as how much each provider focuses on a few standard treatment patterns, or spreads over a variety of pathways (measured by means of a Herfindahl-Hirschman concentration index), as a proxy of the intensity of communications, influences and coordination among clinicians operating in the same ward/clinic.

Main sample descriptive statistics and pairwise correlations of continuous and binary variables are reported in the Appendix.

5. Results

5.1. Sequence analysis of therapeutic switches

We ran optimal alignment on the 619 different therapeutic sequences in our sample, using the various specifications for inter-element weights described in the Methods: transition probabilities between therapies, pharmacological and clinical dissimilarities and, as a benchmark, the simple edit distance with uniform weights. After running optimal alignment, we grouped our sequences based on the resulting distance matrices. We compared the fit of clustering from four common hierarchical algorithms: single, complete, average and Ward's linkages. We chose weights derived from clinical considerations and the average linkage method as the solution that best fit the data.

Table 2 Therapeutic sequences clustering: leader sequences and number of patients in each cluster.

Cluster	Sequence[a]	N	%	Cum
1	2NRTI+1PI 2NRTI+1PI[b]	1 342	44.99	44.99
2	2NRTI+1PI 2NRTI+1PI 2NRTI+1PI	249	8.35	53.34
3	2NRTI	238	7.98	61.31
4	2NRTI 2NRTI+1PI	134	4.49	65.81
5	2NRTI 2NRTI 2NRTI+1NNRTI	112	3.75	69.56
6	2NRTI+1PI 2NRTI+1PI 2NRTI+1PI 2NRTI+1PI	88	2.95	72.51
7	2NRTI+1PI 2NRTI 2NRTI+1PI	88	2.95	75.46
8	2NRTI+1PI 3NRTI	86	2.88	78.34
9-30	Others	646	21.67	100
	Total	2 983	100	

[a] Substitution costs based on clinical and pharmacological differences between drug combinations were set by expert judgment. Factors guiding expert opinion included: number and drug class of the agents in the mix; expected tolerability of each drug combination; unusual combinations not recommended by therapeutic guidelines; mono and dual therapies which were the standard in the pre-HAART era, but are now considered under-performing compared to HAART, and are no longer recommended for treatment; combinations with

[b] NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor. Since the class of NtRTIs is similar to the NRTIs and includes so far only one antiretroviral agent, we included it in the latter.

In order to get small and tightly connected clusters of therapeutic sequences, we set the cut-off value used to form new clusters at a relatively low level of inconsistency. We obtained 238 clusters, for which we chose the central sequences (the medoids of the clusters) as the representative objects. We then ran the partitioning around medoid algorithm on the extracted

sequences to get eventually 30 clusters with their respective leaders (Table 2). Within and between cluster distances were compared with a t-test; the significance testing procedure was an application of the Jackknife technique. The hypothesis of equal distances within and between clusters was rejected at the .01 confidence level; data had been grouped into quite homogeneous and well separated clusters.

As illustrated in Table 2, in most cases the first line treatment was either a dual therapy with two NRTIs or already a HAART regimen containing one PI. Most of the patients starting with a dual therapy switched to HAART afterwards – to a PI-containing or an NNRTI-containing regimen – either directly, or after having tried various dual combinations. Probably due to the low tolerability of PI-containing regimens, or just to the availability of an expanding range of molecules over time, in many clusters we observe several switches among PI-containing therapies, while in others an NNRTI-regimen or a maintenance therapy with 3 NRTIs was preferred.

Mega-HAART with more than three drugs, and HAART with two PIs administered in association, together with anomalous regimens, were usually initiated as salvage therapies (that is, after other regimens had been tried unsuccessfully). The few occurrences of patients sticking to (or even turning again to) mono therapies with one NRTI are to be considered exceptional, whereas cases of subjects switching at least temporally from HAART to dual therapies were more frequent.

Sequence analysis conducted on combination therapies shows that the adoption of the new powerful drug combinations (HAART) proceeded more slowly than expected from their technological superiority, and the emergence of a standard of care, as a coherent pattern of treatment with few alternative strategies, was far from predictable and straightforward.

5.2. Patient and supply-side factors associated to different therapeutic paths

The previous analysis has revealed a significant heterogeneity in individual's treatment histories. This is in sharp contrast with the apparent advantages of HAART technology and cannot be explained as a consequence of patient heterogeneity alone. In order to shed some light on the determinants of divergent therapeutic paths, we performed an exploratory analysis looking for supply-side factors associated with different treatment strategies. The aim of the exercise was to gain some insights into structural and behavioral characteristics of the providers, if any, affecting therapeutic choices together with patient attributes.

We selected as the base choice category of the multinomial logit model estimates the therapeutic sequence where an initial HAART (a single PI or NNRTI containing regimen) was followed by a new HAART formulation, and we labeled it simply *HAART*. Relative to this standard, which accounts for 45% of our sample, we identified two opposite pathways, one in which the individual never started HAART, but instead continued a dual therapy, and another in which the subject often switched to HAART only after trying several dual combinations (accounting together for 16% of the sample), which we called a *pre-HAART* and a *switching-to-HAART* treatment pattern, respectively. All other patterns, characterized by less straightforward histories, with many therapy switches, and sometimes quite uncommon drug combinations, were grouped into a single residual category.

Regression results are shown in Table 3. Individual characteristics were selected according to the clinical literature on factors driving therapeutic choices (as summarized, for instance, by the

U.S. Treatment Guidelines). Among demographic factors we found that women were more likely than men to start with a dual therapy and to follow an idiosyncratic therapeutic path. This result can be associated to women being more likely than men to discontinue antiretroviral therapies due to toxicity and to women starting AZT mono therapy during pregnancy. Early stages of the disease and a less aggressive infection (higher CD4 cells count and lower viral load level)[1], as well as Hepatitis-C co-infection (HCV+), were associated to a greater probability of starting and remaining on a dual therapy compared to HAART. The number of virological treatment failures (episodes of detectable viremia after therapy initiation) was positively associated with having a non standard treatment history, both because they were more frequent among patients following a pre-HAART therapy, and usually led to therapy switching toward different and sometimes unusual combinations.

These factors all relate to patient heterogeneity in baseline characteristics and response to therapy, and obviously play a major role in determining treatment strategies. We were interested in understanding whether there is also a place for explaining factors associated to the evolution of the technology and the characteristics of providers as potential adopters. First of all, the enrolment period was strongly associated with treatment history: the marginal effect of entering the cohort during the second round of enrolments on the probability of ending up with a standard treatment path was 0.22. Those enrolled in the year 2000 or after were less likely to follow a non standard pattern of therapies due both to the diffusion of HAART as a technological standard and to the shorter follow-up time. This, in turn, may indicate that the gradual advancements in HAART technology have had an appreciable impact on the probability of adoption of the new standard of care.

In addition, the number of scientific publications was negatively associated with the probability of staying on dual therapies instead of switching to HAART (the effect of one standard deviation increase from the mean number of scientific publications on the probability of being in our base outcome category was 0.06). This result confirms the importance for the diffusion of innovations of channels allowing the open communication of productive knowledge within the medical profession.

Finally, high concentration levels on common treatment strategies among practitioners belonging to the same clinical center were less likely to lead to under-performing pathways with dual therapies instead of HAART or to idiosyncratic therapeutic histories. We observed a positive effect of 0.22 on the probability of following a standard therapeutic pattern for one standard deviation increase from the mean of the Herfindahl-Hirschman index. High concentration of therapeutic strategies at the provider level can be considered an indicator of the intensity of coordination and exchange of information among local practitioners. This finding points to the impact of bureaucratic organizational mechanisms, interacting with doctors' professional autonomy, on the diffusion of innovations.

[1] We always took the square root of CD4 cell counts, and the log base ten of plasma HIV-RNA levels to be included in our regression models, in order to account for the skewed distributions of these variables.

Table 3 Multinomial logit estimates of patient and provider characteristics associated to main therapeutic paths.

		RRR[a]		
Outcome *HAART is the comparison group* (2NRTI+1PI 2NRTI+1PI)		*pre-HAART* (2NRTI)	*switching-to-HAART* (2NRTI 2NRTI+1PI or 2NRTI 2NRTI 2NRTI+1NNRTI)	*Other*
CD4+ (square root cells/mm^3)		1.053***	1.030**	1.002
		(0.014)	(0.012)	(0.008)
HIV-RNA (log_{10} copies/ml)		0.692***	0.815**	1.060
		(0.070)	(0.076)	(0.071)
HCV+		1.479**	1.592***	1.195
		(0.259)	(0.249)	(0.136)
Detectable viremia episodes		1.153***	1.202***	1.202***
		(0.023)	(0.021)	(0.018)
Woman		1.223	1.438**	1.615***
		(0.232)	(0.242)	(0.195)
Enrolment period II		0.234***	0.124***	0.546***
		(0.086)	(0.053)	(0.081)
Size		0.990	1.000	0.998
		(0.008)	(0.007)	(0.005)
Specialization in HIV care		1.636	1.084	0.916
		(0.837)	(0.515)	(0.278)
Genotypic assessment		0.880	0.795	1.000
		(0.288)	(0.242)	(0.188)
Publications		0.981***	0.991*	0.994
		(0.007)	(0.005)	(0.004)
Multi-center studies		1.021	0.992	1.009
		(0.017)	(0.015)	(0.010)
HHI (0-100]		0.969***	0.967***	0.966***
		(0.009)	(0.008)	(0.005)
N	2 163			
Log-likelihood	-2 209.59			
Likelihood-Ratio chi-squared (36)	700.23***			

[a] Relative Risk Ratio. Standard errors in parentheses. *p < 0.10 **p < 0.05 ***p < 0.01

5.3. Health outcomes and costs of different therapeutic paths

Having examined the emergence of new therapeutic strategies coming with the diffusion of innovative health technologies we turned to the analysis of the associated health outcomes. In particular, we were interested in understanding whether departures from the identified standard of care, resulting from autonomous medical decisions, led to inferior outcomes in terms of clinical endpoints.

Table 4 Cox proportional hazards model estimates of time to AIDS/death on patient characteristics and therapeutic path.

Time to AIDS/death	**HR**[a]
CD4+ (square root cells/mm^3)	0.939***
	(0.012)
HIV-RNA ($\log_{10}$ copies/ml)	1.304***
	(0.124)
CDC stage B	1.241
	(0.212)
HCV+	0.798
	(0.149)
Exposure category[b]	
Homosexual	0.333***
	(0.090)
Heterosexual	0.319***
	(0.072)
Other	0.585
	(0.192)
Woman	1.046
	(0.185)
Age (years)	1.028***
	(0.009)
Treatment pattern	
pre-HAART	1.597*
	(0.388)
switching-to-HAART	0.865
	(0.207)
Other	0.590***
	(0.099)
(reference: HAART)	
N	2 377
Log-likelihood	-1 413.05
Likelihood-Ratio chi-squared (12)	134.52***

[a] Hazard ratios. Standard errors in parentheses. *p < 0.10 **p < 0.05 ***p < 0.01

[b] Reference category: Intravenous drug user

Table 4 reports Cox proportional hazards estimates of time to full-blown AIDS or death adjusted for clinical and immuno-virological parameters at baseline, Hepatitis C co-infection, exposure category, gender, and age at enrolment (see, e. g., Egger et al., 1997), together with the treatment pattern followed by each subject in the sample (patient diagnosed with AIDS at enrolment were of course excluded from the analysis).

There was some evidence of patients on dual therapies being more likely to progress to full-blown AIDS or death than those in our reference category (starting HAART as first line regimen and switching therapy at most once), while subjects in the residual group, with non-standard treatment histories, were progressing to AIDS/dying at a lower rate than those in the comparison group (hazard ratios equal to 1.60 and .59, respectively). Older individuals had a higher hazard rate, as expected, as well as more debilitated patients (with lower CD4 cells count and higher viral load). Exposure category was also related to disease progression and survival.

An important caveat concerns the limited length of the study: we observed six years in the life of the cohort, which provide only medium-run evidence of disease progression for what is nowadays becoming a chronic infection.

Cohort subjects with non-standard treatment histories, are experiencing better clinical outcomes than those following a standard treatment path. In highly complex technological enviroments with moving technologies and strong uncertainty, decentralized professional decision making results in better outcomes in the management of technological innovations.

Table 5 OLS estimates of log average annual costs on patient characteristics and therapeutic path

Log average annual costs	**Coefficient**[a]
CD4+ (square root cells/mm^3)	-0.023***
	(0.002)
HIV-RNA ($\log_{10}$ copies/ml)	0.080***
	(0.019)
HCV+	-0.062**
	(0.028)
Detectable viremia episodes	0.062***
	(0.007)
Square of detectable viremia episodes	-0.002***
	(0.000)
New AIDS Defining Events	0.163***
	(0.048)
Square of New AIDS Defining Events	-0.032***
	(0.012)
Inpatient admissions	0.237***
	(0.025)
Enrolment Period II	0.215***
	(0.049)
Treatment pattern	
pre-HAART	-0.473***
	(0.060)
switching-to-HAART	-0.048
	(0.037)
Other	0.049*
	(0.028)
(reference: HAART)	
Constant	8.382***
	(0.114)
N	2 818
F(44, 2 773)	28.31***
R-squared	0.316

[a] Standard errors in parentheses. *p < 0.10 **p < 0.05 ***p < 0.01

We integrated the previous analysis of health outcomes with an examination of the costs incurred in treating a sub-sample of 2 818 patients, for which full baseline and follow-up information was available. In a multivariate regression of log annual direct health costs (yearly averages over patients' follow-up period in 1997 constant prices) the OLS estimated coefficient of therapeutic pathway category for patients remaining on dual therapy was negative and significant[2]. The coefficient of the treatment category including subjects who switched to HAART after following a dual therapy, was still negative (although the absolute value was much lower) but not statistically significant, while that of the residual pattern category was positive and only slightly significant.

Regressors included controls for baseline medical conditions (immunological and virological values at baseline) and follow-up adverse events (virological treatment failures, new AIDS Defining Events occurring in the course of therapy, and number of inpatient admissions) that might affect total health costs independently of antiretroviral therapy administration. Coefficient estimates for all independent variables are reported in Table 5 with White-robust standard errors to account for heteroskedasticity. In the regression we also controlled for health provider using a stepwise procedure (coefficients are omitted from the results).

Estimates of the annual costs in the log scale, evaluated at the mean of the continuous covariates, for a HCV-negative individual enrolled during the first enrolment period (with no adjustment for health provider) were equal to 8.275, 7.802, 8.227, and 8.324, corresponding to median raw costs of 3 924 euro for the reference group, and 2 445, 3 739, and 4 122 euro for the other therapeutic patterns, respectively.

Suboptimal treatment patterns (i.e., persistent dual therapies) led to worse clinical endpoints and were associated to lower health expenditures, whereas non-standard therapeutic histories favored better health outcomes at no extra costs for the health care budget.

6. Conclusions

In this study we contributed to the analysis of medical innovations highlighting the evolving nature of technologies themselves, along with the interplay of the different actors involved at the individual or more aggregate level, which together led to complex patterns of adoption and implementation in our empirical setting.

Sequence analysis methodology allowed us to describe in detail HIV-positive patients' whole treatment histories, privileging an analytic representation to a synthetic focus on specific features of HIV therapies. We found that the high variety observed in therapeutic paths can be only partly explained by observable patient characteristics. An important role is also played by continuous technological progress and providers' activities and routines. Still, a major component of treatment heterogeneity seems to be related to the idiosyncratic behavior of every single physician, the individual patient reaction to treatment, and the interaction between patient and provider's medical staff.

Standardization seems to have occurred at a lesser extent than we might have predicted looking at scientific advances and leading opinions. Treatment guidelines, which sometimes lag behind the introduction of innovations, do not (and, actually, cannot) cover the entire set of therapy

[2] Health care expenditure data are typically highly skewed and not normally distributed. A small number of large cost observations can have a critical impact on the size of the estimated parameters and their significance when regressing raw costs data on potentially related covariates. Logarithmically transforming health care expenditure data can reduce the influence of outlier observations and make traditional statistical assumptions more plausible. In our data the mean of the raw annual costs was 7 310 euro, while the median was 5 879 euro, and the skewness 41.57. That is, right tail skewness was substantial, with the median being much smaller than the mean, and the measure of skewness being positive and large. However when cost data were log-transformed, skewness fell close to zero – actually, it was slightly negative (-1.59, variance = .70).

administration issues. Even on those topics covered by treatment guidelines, clinical decisions have been taken more with regard to the practical circumstances faced by medical professionals in their everyday activity, and to the local practice adopted by the clinical center. So far heterogeneity among treatment pathways has proved beneficial from the effectiveness side, and has not led to significantly higher health expenses.

The variability observed in HAART adoption patterns across clinical centers, both in terms of the pace of adoption of new drugs and the preference accorded to specific combination therapies and/or their sequences, resulted in a slower overall process of adoption of this new technology than would be expected from its highly improved efficacy. This effect may have been emphasized by an underlying inertia, coming in this case from a conservative strategy of prosecution along the lines of a less aggressive pre-HAART regimen in patients still in early stages of the disease.

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Appendix Sample descriptive statistics and correlations.

	Woman	HCV+	Enrolment	Geno-assay	CD4+	HIV-RNA	Failures	ADEs	Inpatient	Age	Size	HIV care	Publications	Studies	HHI
Woman	1.000														
HCV+	-0.063	1.000													
Enrolment period II	0.021	-0.159	1.000												
Genotypic assessment	0.129	-0.045	0.109	1.000											
CD4+ (square root cells/mm^3)	0.063	0.053	-0.190	-0.016	1.000										
HIV-RNA (log_{10} copies/ml)	-0.103	-0.036	0.174	-0.007	-0.406	1.000									
Detectable viremia episodes	-0.017	-0.025	-0.308	-0.102	0.043	0.045	1.000								
New ADEs	-0.019	0.003	-0.042	0.028	-0.188	0.119	0.030	1.000							
Inpatient episodes	0.004	0.030	-0.011	0.059	-0.278	0.207	0.060	0.587	1.000						
Age	-0.162	-0.105	0.051	-0.029	-0.140	0.089	-0.018	-0.005	0.040	1.000					
Size	-0.026	-0.037	-0.071	0.176	0.072	-0.108	0.117	0.003	0.051	-0.053	1.000				
Specialization in HIV care	0.146	-0.084	0.122	0.109	-0.097	0.104	0.031	0.028	0.033	-0.046	-0.105	1.000			
Publications	-0.039	-0.073	0.030	-0.180	-0.005	-0.076	0.191	-0.037	0.008	0.006	0.082	0.188	1.000		
Multi-center studies	0.010	-0.063	0.055	-0.052	0.027	-0.065	0.005	-0.001	-0.040	-0.008	0.122	-0.100	-0.071	1.000	
HHI	0.082	-0.021	0.187	0.327	-0.138	0.128	-0.257	0.043	0.025	-0.049	-0.180	0.301	-0.138	-0.201	1.000
N	2 983	2 983	2 983	2 983	2 976	2 837	2 983	2 983	2 983	2 983	2 983	2 566	2 489	2 482	2 983
Min	0.00	0.00	0.00	0.00	0.00	1.30	0.00	0.00	0.00	0.00	0.00	0.01	2.00	2.00	10.61
Max	1.00	1.00	1.00	1.00	41.90	7.15	37.00	8.00	12.00	98.00	59.00	0.97	84.00	25.00	76.33
Mean	0.31	0.38	0.20	0.14	17.14	4.55	5.03	0.13	0.40	36.93	24.99	0.32	16.75	11.34	26.61
SD					7.36	0.91	5.64	0.53	0.91	8.57	10.69	0.20	15.82	5.66	12.55