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First-line HIV treatment: evaluation of backbone choice and its budget impact

ORIGINAL RESEARCH

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ABSTRACT

OBJECTIVE: The gradual increase of persons living with HIV, mainly due to the reduced mortality achieved with effective antiretroviral therapies, calls for increased rationality and awareness in health resources consumption also during the early illness phases. Aim of this work is the estimation of the budget impact related to the variation in backbone prescribing trends in naïve patients.

METHODS: Target population is the number of patients starting antiretroviral therapy each year, according to the Italian HIV surveillance registry, excluding patients receiving non-authorized or non-recommended regimens. We modeled 3-year mortality and durability rates on a dynamic cohort, basing on international literature. A prevalent patients analysis has also been conducted, for which the model is fed by a closed cohort consisting of all the patients without experience of virologic failure. The aim of this collateral analysis is to estimate the difference in current annual expenditures if the past prescription trends for patients starting therapy would have led to the evaluated hypothetical scenarios. Current Italian market shares of triple regimens containing first-choice or alternative backbones (tenofovir/emtricitabine, abacavir/lamivudine, tenofovir/lamivudine and zidovudine/lamivudine) are compared to three hypothetical scenarios (base-case, minimum and maximum) in which increasing shares of patients eligible to abacavir/lamivudine start first line treatment with this backbone. Annual cost for each regimen comprises drugs acquisition under hospital pricing rules, monitoring exams and preventive tests, valued basing on regional reimbursement tariffs.

RESULTS: According to current prescribing trends, in the next three years about 13,000 patients starting HIV therapy will receive tenofovir/emtricitabine (83% of the target population), and minor portions other regimens (9% abacavir/lamivudine, 8% zidovudine/lamivudine). Patients that would be eligible to abacavir/lamivudine are 1.5, 4.5 and 6 thousand more than those presently treated according to the three hypothetical scenarios, leading to a cumulative saving of 850 thousand, 2.4 million and 3.3 million euro, respectively. If in the past the same modification of first line prescription trend was adopted, the annual current cost saving would vary from 922 thousands to 7.3 million euro. Most of this amount is due to reduced acquisition costs and, secondarily, to lower monitoring needs.

CONCLUSION: Where patient features don't force the choice of the backbone, abacavir/lamivudine prescription may induce substantial savings, allowing the release of resources needed to manage more complicated/advanced cases.

Keywords

HIV; Budget Impact; Antiretroviral therapies; Abacavir

INTRODUCTION

The correct moment and regimen for starting HIV antiretroviral therapy has been debated since the concept of HAART (Highly Active Antiretroviral Therapy) was introduced. In general, regimen selection should be individualized based on a number of factors, including co-morbidity conditions, resistance, potential adverse drug effects, drug interactions, pregnancy, CD4 count, tropism assay and specific tests, and administration convenience. Very briefly, according to Italian Guidelines [1] those regimens studied in randomized controlled trials and shown to have durable virologic efficacy, favourable tolerability profiles, and ease of use are defined as first choice. Alternative are effective treatments that present some potential disadvantages if compared with preferred regimens. They may be a valid choise in certain situations and based on individual patient needs. Some other regimens are classified as "not recommended " because of reduced virologic activity, lack of supporting data from

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large clinical trials, or other factors, such as toxicities, administration schedule, etc.

An initial HAART regimen generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) as backbone and a third drug consisting of a protease inhibitor (PI), preferably "boosted" with ritonavir, or a non-nucleoside reverse transcriptase inhibitor (NNRTI). More recent third drug classes, like INSTI (integrase strand transfer inhibitors) are very effective, but more expensive compared to the older ones; so their use is still limited. The two backbones recommended as first choice in the Italian Guideline are tenofovir/emtricitabine, in fixed combination with efavirenz or not, and abacavir/lamivudine, for viral loads <100.000 copies per millilitres. The combination of tenofovir/lamivudine (non-available as one-pill co-formulation) and of lamivudine/zidovudine are considered as alternative backbones. Didanosine-based backbones are defined "not recommended" strategies. Guidelines suggest to also take in account the presence of specific factors when taking backbone decisions: renal and bone co-morbidities advise against tenofovir prescription, while abacavir may be employed only in HLA-B*5701 negative patients. Three randomized trials have compared abacavir/lamivudine and tenofovir/emtricitabine [2-4] on almost 3,000 HIV patients. Two of these involved treatment-naive patients [3,4]. Two trials found similar efficacy, while Sax and colleagues found better efficacy with the tenofovir-based regimen in those patients with > 100,000 copies/ml [4]. All the trials had the strong limitations of not having excluded patients positive for HLA-B*5701 antigen, which mediates hypersensitivity event, and of not having evaluated bone mineral density.

Reviews of real prescription data and expert opinion indicate that often it is the third drug choice that drives regimen selection in the clinical management of HIV patients when starting HAART. This behaviour is mainly due to resistance issues, prescribing experience or spending containment. A common problem of both clinical and administrative hospital decision makers is indeed the need to combine clinical efficacy and economic affordability; one way to get to this objective is targeting the prescription choice in order to contain the expense for patients that well respond to cheaper treatments and, concurrently, save the financial funds for difficult patients. We planned to investigate how the financial impact of the antiretroviral first line treatment in Italy may change as a result of a variation in backbone prescription, keeping the third drug choice constant. At this aim we built a decision-analytic Budget Impact Model (BIM) that estimates the number of treatment-naive HIV patients that every year start HAART, their distributions among first choice (and alternative) regimens in the real context, and the expenditure changes of hypothetical prescription trend modifications to show the amount that the National Health Service could potentially save and dedicate to the portion of complex HIV cases.

METHODS

Model characteristics

The presented BIM is programmed to answer two questions: what is the financial impact on the Italian National Health Service of changing the current backbone prescription trend for patients starting HAART? How much could be annually saved (or paid) if, in the past, the first line prescription trend had been different? In both cases, the third drug market share is kept constant. To answer the first question, we ran the analysis on an open cohort of incident to therapy patients, over a three year time horizon. This incidence with accumulation methodology is the most appropriate to simulate chronic illnesses on medium-long time horizons, according to the international Budget Impact Analysis guideline [5]. The second question is answered by means of the prevalent simulation, in which the model is fed by a closed cohort consisting of all the patients receiving HAART therapy in Italy that have not experienced virologic failure yet (first line + switched for tolerability patients) over a single year time horizon. In both simulations, the very same cohort is virtually assigned to the current scenario, that represents the real patient distribution among selected regimens, and to the hypothetical scenario, representing the prescription variation we would like to evaluate. The cost ascribed to each scenario comprises pharmaceutical and laboratory costs. The analysis considers both the national and the regional contexts.

Incident patient pool simulation

Patient flow

For the first year, the model is fed with the pool of patients that annually begin HAART (incident to therapy); the next year the cohort consists of alive and persistent first year-patients, to which the new cases pool is added. The same reasoning is applied for the third year. One of the most challenging tasks required to define the patient flow is the estimate of the annual rate of HAART starting. It is a fact that only a fraction of new HIV diagnoses is immediately followed by therapy start.

However, in the present model we consider no difference between HIV incidence and incidence to therapy rates; this choice is based on the assumption that both the HIV incidence and the mean lag between diagnosis and therapy beginning are quite constant over the short time horizon considered. According to this postulation, the portion of patients receiving diagnosis in the past years that begin treatment in the year of the analysis is similar to that of patients receiving diagnosis in the year of analysis that will start the therapy in the future. Only first choice and alternative regimens are considered: patients starting HAART with not recommended/not authorized regimens are excluded from the simulated cohort. The patient flow input data for the incident pool simulation are summarized in Table I.

New diagnoses incidence rate is taken from the national AIDS database updated to 2009 [6] and applied to current resident population of each region [10]. Mortality rate is assigned to HIV patients in function of the cumulative time in therapy, based on data of an european observational multicenter study [8]. The persistence in therapy corresponds to the durability of the treatment till virologic failure; it has been assumed homogeneous among regimens and exclusively dependent on the time in therapy. This choice is made to avoid two confounding effects: the paradox effect of inducing higher costs for strategies with major durability, and the masking effect of producing BIM results influenced not only by the cost of the regimen, but also by different numbers of treated patients. We estimated this common persistence rate by means of a Bayesian random effects meta-analysis on durability data of the main HAART regimens, as collected by Colombo and colleagues [9].

Input data			Source
HIV incidence rate (n diagnosis/ 100.000 habitants/year)	Italia*	5.68	ISS, 2011 [6]
	Piemonte	6.8	
	Valle d'Aosta	7.9	
	Lombardia	6.4	
	Trentino-Alto Adige	4.7	
	Veneto	4.4	
	Friuli-Venezia Giulia	2.8	
	Liguria	6.4	
	Emilia-Romagna	9.3	
	Toscana*	5.7	
	Umbria	4.8	
	Marche	5.6	
	Lazio	9.0	
	Abruzzo	6.0	
	Molise*	5.7	
	Campania*	5.7	
	Puglia	2.9	
	Basilicata*	5.7	
	Calabria	1.6	
	Sicilia	3.2	
	Sardegna	2.7	
Patients excluded for regimen (%)		10.79	IMFO, 2011-2012 [7]
HIV patients mortality (%)	After 1 year of therapy	1.70	Murray, 2011 [8]
	After 2 years of therapy	2.64	
Persistence in therapy (%)	After 1 year of therapy	75.5	Elaborated from Colombo, 2011 [9]
	After 2 years of therapy	64.2	

Table I. *Incident patients analysis: patient flow input data*
* Elaborated as average of the regions with available data

Prescription scenarios

Current prescription tendency in Italy for patients that start HAART is shown in Table II. It's estimated based on sales data [7], with restriction to:

- First-line therapy;
- HAART beginning between March 2011 and February 2012 (to avoid seasonal time bias on recorded market shares);
- First ten regimens for each backbone (of which only recommended ones are considered).

Regimens basing on tenofovir/lamivudine in extemporary association (co-formulation is not available on the market) is prescribed in an undetectable portion of patients in our sample of sales. For the Regional analyses,

Backbone	MS	RAL	DRV/r	ATV/r	LPV/r	EFV	NVP	fAPV/r
ABC/3TC (%)	**8.97**	1.47	21.69	49.27	10.17	10.17	5.76	1.47
TDF/FTC (%)	**82.98**	0.75	25.37	25.96	8.76	38.23*	0.92	0.00
AZT/3TC (%)	**8.05**	0.00	4.80	8.01	61.36	8.11	16.12	1.60
TDF + 3TC (%)	**0.00**	-	-	-	-	-	-	-
Weighted mean (%)		**0.75**	**23.38**	**26.61**	**13.13**	**33.29**	**2.58**	**0.26**

Table II. *Incident analysis: current scenario prescription data*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; MS = Market Share; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir
* Of which 59% co-formulated (Atripla®)

data for each backbone are available, but not detailed by line of treatment, so these values are estimated by matching regional overall backbone prescription with the between-lines relative frequencies recorded in the National setting

Hypothetical scenarios, as previously defined, represent variations in prescription trends whose effect we would like to evaluate. Four main constraints condition our hypothetical settings:

- Tenofovir/emtricitabine and abacavir/lamivudine are the only two guideline- recommended first choice backbones;
- Their effectiveness has been shown similar for < 100,000 copies/ml patients;
- Third drug market shares have to be maintained on average constant in the two scenarios;
- Abacavir is not recommended in patients positive for HLA-B*5701 allele.

Patients with less than 100,000 copies/ml before therapy start and negative for HLA-B*5701 allele are indicated to receive abacavir/lamivudine as backbone (Table III). Some observational data show that viral loads below this threshold are present in about 70% of treatment-naive patients [11-13]. Recent Italian data [14,15] indicate lower values (under 50%, assuming a uniform distribution between median and Q3). We conservatively assumed a base case scenario in which this portion is set to 40%, testing the sensitivity of our results to this assumption with minimum and maximum scenarios, in which only 20% and up to 50% of patients present low viral loads, respectively. The prevalence of the allele associated to abacavir hypersensitivity is taken from a study pooling the results of six multicenter trials on its frequency in the patient population, measured independently from treatment received or previous screening [16]; for our country the prevalence resulted equal to 6%. Matching these considerations, we constructed hypothetical scenarios reported in Table III.

	Backbone – Market Share			
	ABC/3TC (%)	TDF/FTC (%)	AZT/3TC (%)	TDF + 3TC (%)
Base-case scenario	37.60	54.35	8.05	0.00
Minimum scenario	18.80	73.15	8.05	0.00
Maximum scenario	47.00	44.95	8.05	0.00
Third drug				
RAL	0.75%			
DRV/r	23.38%			
ATV/r	26.61%			
LPV/r	13.13%			
EFV	33.29%			
NVP	2.58%			
fAPV/r	0.26%			

Table III. *Incident analysis: hypothetical scenarios prescription data*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir

Input data			Source
Prevalent Italian HIV patients (n.)	Italia	61,175	IMFO, 2011-2012 [7]
	Piemonte	3,820	
	Valle d'Aosta	60	
	Lombardia	18,603	
	Trentino-Alto Adige	642	
	Veneto	4,059	
	Friuli-Venezia Giulia	779	
	Liguria	2,352	
	Emilia-Romagna	7,235	
	Toscana	3,861	
	Umbria	727	
	Marche	1,377	
	Lazio	8,656	
	Abruzzi	575	
	Molise	71	
	Campania	1,921	
	Puglia	2,141	
	Basilicata	118	
	Calabria	385	
	Sicilia	2,275	
	Sardegna	1,518	
	Other		
No virologic failure patients (%)		70.90	Market survey - Data on file
Patients excluded for regimen (%)		10.00	IMFO, 2011-2012 [7]

Table IV. *Prevalent analysis: patient flow input data*

Prevalent patient pool

Patient flow

The analysis on the prevalent cohort, as anticipated, aims to estimate how much it would annually cost to treat prevalent HIV patients never yet experiencing a virologic failure, with the hypothetical prescription patterns as compared to the real one. It has not the objective to make future previsions, but to inform on the potential difference in annual costs in the case in which the prescription trend for incident patients accumulating over time had been such to observe today the hypothetical scenario in the current prevalent first line population. The total number of prevalent Italian HIV patients is calculated based on backbone consumption (Table IV), under the assumption that each patient doesn't receive more than one backbone regimen.

Target population is determined by the portion of total prevalent Italian HIV patients

Backbone	MS	RAL	DRV/r	ATV/r	LPV/r	EFV	NVP	fAPV/r
ABC/3TC (%)	14.74	1.77	7.15	39.00	14.08	15.69	13.74	8.57
TDF/FTC (%)	76.30	1.88	10.47	22.24	12.18	41.87	7.68	3.68
AZT/3TC (%)	7.30	0.68	1.09	4.43	38.85	10.61	40.59	3.75
TDF + 3TC (%)	1.66	0.00	4.88	19.58	28.45	19.64	20.61	6.84
Weighted mean (%)		1.74	9.20	23.37	14.68	35.36	11.19	4.46

Table V. *Prevalent analysis: current scenario prescription data*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; MS = Market Share; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir

Drug	Daily dose	Packaging	Monthly H cost (€)	Source
ABC (Ziagen®)	600 mg	60 tab 300 mg	224.40	LG 2012 [1], PDT 2012 [18]
ABC/3TC (Kivexa®)	1 tab	30 tab 600/300 mg	398.31	
ATV (Reyataz®)	300 mg	30 cps 300 mg	332.97	
DRV(Prezista®)	800 mg	60 tab 400 mg	348.48	
EFV (Sustiva®)	600 mg	30 tab 600 mg	214.50	
FTC* (Emtriva®)	200 mg	30 tab 200 mg	161.48	LG 2012 [1], IF 2012 [19]
fAPV (Telzir®)	1,400 mg	60 tab 700 mg	316.14	LG 2012 [1], PDT 2012 [18]
3TC (Epivir®)	300 mg	30 tab 300 mg	86.46	
LPV/r (Kaletra®)	800/200 mg	120 tab 200/50 mg	357.72	
NVP (Viramune®)	400 mg	60 tab 200 mg	188.10	
RTV (Norvir®)	100 mg	84 cps 100 mg	24.90	
RTV (Norvir®)	200 gm	84 cps 100 mg	49.94	
RAL (Isentress®)	800 mg	60 tab 400 mg	521.40	
TDF (Viread®)	245 mg	30 tab 245 mg	276.87	
TDF/FTC/EFV (Atripla®)	1 tab	30 tab 245/200/600 mg	653.40	
TDF/FTC (Truvada®)	1 tab	30 tab 245/200 mg	438.90	
AZT (Retrovir®)	600 mg	60 tab 300 mg	123.75	
AZT/3TC (Combivir®)	600/300 mg	60 tab 300/150 mg	313.50	

Table VI. *Dosage and price of drugs considered in the model*
*Not present in [18]
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV/r = lopinavir;/ritonavir NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir

that are in the first line of treatment or that switched therapy for tolerability reasons (no virologic failure), with the further exclusion of patients receiving regimens composed by four or more drugs.
As in the incident pool simulation, only first choice and alternative regimens are considered.

Prescription scenarios

The current distribution among first choice regimens of the prevalent target population (no virologic failure patients) is shown in Table V. It's estimated based on sales data [7], considering:

- First-line treatment + switched for tolerability reasons patients;
- No time restriction for HAART beginning;
- First ten regimens for each recommended backbone.

Hypothetical scenario inputs follow the same reasoning and assumptions of the analysis on incident patients: market shares of abacavir/lamivudine are set on 18.80%, 37.60% and 47%, respectively for minimum, base-case and maximum scenario, with a corresponding switch of patients from tenofovir/emtricitabine.

Economical inputs

Cost of each regimen is estimated according to the following scheme.

Direct costs = preventive tests + Pharmaceutical + Monitoring

Pre-treatment costs

Italian and international guidelines [1,17] recommend specific laboratory and clinical exams before starting HAART to test the sui-

Adverse event/ co-morbidities	Exam brief description	National unit cost (€)
Abacavir hypersensivity	HLA-B*5701 test	56.23
Hepatic functioning	Hepatic enzimes	8.52
	Bilirubin level	2.54
Cardiovascular disease	Electrocardiogram	12.03
Bone dysfunction	Bone metabolism biomarkers	65.67
	Lumbar spine and hip DEXA	33.45
Renal functioning	Urine, creatinine, electrolytes	14.28
Dyslipidemia	Lipids profile	7.24
Diabetes	Glycaemia	1.55

Table VII. *Unit costs of preventive and monitoring examinations. Source: Nom Spec, 2009 [20]*

	Patient (n.)
Residents	60,626,442
Incident HIV patients	3,445
Excluded for regimen	372
Year 1 target population	**3,074**
Deaths	52
Dropped-out	740
New incident patients	3,074
Year 2 target population	**5,355**
Deaths	81
Dropped-out	1,073
New incident patients	3,074
Year 3 target population	**7,275**
Cumulative patient-year	**15,703**

Table VIII. *Flow for incident patients analysis*

Regimens	Prescriptions (n.)	
	Current scenario	Base case hypothetical scenario
ABC/3TC/RAL	21	45
ABC/3TC/DRV/r	306	1381
ABC/3TC/ATV/r	694	1,571
ABC/3TC/LPV/r	143	775
ABC/3TC/EFV	143	1,965
ABC/3TC/NVP	81	152
ABC/3TC/fAPV/r	21	15
TDF/FTC/RAL	98	64
TDF/FTC/DRV/r	3,306	1,996
TDF/FTC/ATV/r	3,383	2,271
TDF/FTC/LPV/r	1,143	1,121
TDF/FTC/EFV*	4,982	2,841
TDF/FTC/NVP	120	220
TDF/FTC/fAPV/r	-	22
AZT/3TC/RAL	-	10
AZT/3TC/DRV/r	61	296
AZT/3TC/ATV/r	101	336
AZT/3TC/LPV/r	776	166
AZT/3TC/EFV	103	421
AZT/3TC/NVP	204	33
AZT/3TC/fAPV/r	20	3

Table IX. *Incident patients distribution among considered regimens*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir
* Of which 2,959 in the current and 1,687 in the hypothetical receive co-formulation Atripla®

tability of the chosen first line regimen, in addition to routine cells count and viral load investigations. Based on guideline indications, a panel of experts identified which of these are typically carried out in an Italian real clinical practice setting; only the determination of the allele associated to abacavir hypersensitivity resulted generally adopted. Italian (and local) current tariff of direct sequencing is used as proxy of the real cost of materials and work time to perform HLA-B*5701 genomic typing (Table VII).

Pharmaceutical cost

Since considered drugs are supplied by the hospital pharmacy, real prices paid by a big hospital located in the northern part of Italy are used to inform the budget impact analysis [18]. They correspond to VAT-inclusive ex-factory prices, net of hospital discounts according to the negotiation process (Table VI). To calculate daily and monthly cost, dosage and frequency are taken from the Italian guideline [1].

Monitoring cost

Guidelines strongly recommend carrying out periodical exams to evaluate non-infective co-morbidity onset in HIV patients, especially if they are treated with specifically toxic drugs. These recommendations have been reviewed by a panel of experts that drive us to the understanding of which tests and how often are usually performed in real clinical practice.

The following list summarizes the monitored co-morbidities and the regimen-specific frequency adopted for our model:

- Hepatopathy: liver enzymes dosing 2 times/year for all patients; bilirubin level assessment 3 times/year for patients receiving atazanavir;
- Cardiovascular disease: electrocardiography 1 time/year for all patients;
- Ostheopathy: analysis of bone metabolism biomarkers (serum osteocalcin, parathyroid hormone, telopeptide, phosphorus and calcium) 1 time/year for patients receiving tenofovir; dual energy x-ray absorptiometry (DEXA) scan of lumbar spine and hip, 2 times/year for all patients;
- Renal functioning: complete urine exam, creatinine, blood electrolytes 1 time/year for all patients, 2 times/year for patients receiving atazanavir or lopinavir, 3 times/year for those receiving tenofovir;
- Dyslipidemia: lipid profile 1 time/year for all patients, 2 times/year for patients receiving abacavir, 3 times/year for those receiving a protease inhibitor;
- Diabetes: glycaemia assessment 1 time/year for all patients, 2 times/year for pa-

tients receiving abacavir, 3 times/year for those receiving a protease inhibitor;

Unit cost for monitoring exams is taken from current National and local reimbursement tariffs [20] (Table VII).

RESULTS

Patients results

Every year in Italy, about three thousand patients are estimated to start HAART, of which 2,300 stay on the same first line therapy for the following year, and about 1,900 for the third consecutive year. The incidence with accumulation approach leads to the gathering of a target population of 7,300 patients, for the third year of the analysis. Table VIII summarizes the incident patient flow over time; a total of 15,703 patients have been treated for 1 year. Table IX shows the patient distribution among considered regimens, according to the scenario. In the base case hypothetical scenario, tenofovir/emtricitabine backbone loses almost 4.5 thousand patients in favour of abacavir/lamivudine, while the others remain quite stable. The largest increase in market share regards abacavir/lamivudine/efavirenz-based therapy that passes to be assigned to 143 patients over three years in current practice to a 14-fold larger group, under the tested hypothesis. Efavirenz is the most used drug in association to tenofovir/emtricitabine, so the hypothesized market inversion between this regimen and that based on abacavir/lamivudine may explain this result, combined with the basilar assumption that, on average, the third drugs prescription prevalence has to be maintained stable, independently from the chosen backbone. Also regimens consisting of abacavir/lamivudine added to lopinavir or darunavir present very strong (5-fold) market share increases.

The Italian prevalent HIV patients are more than 60 thousands, and more than two-thirds haven't ever had a virologic failure. Every year in Italy about 39 thousands HIV patients are treated with a first line therapy, comprising strategies changed for tolerability reasons and excluding those patients receiving non-recommended regimens (Table X). As shown in Table XI, main market share modifications, in function of the base case scenario, follow the same trend of incident patients analysis, with abacavir/lamivudine backbone "gaining" 8,900 patients, lost by tenofovir/emtricitabine. The differences are relatively less deep than in the incident patients analysis, since the distribution of prevalent patients among backbones is slightly more equilibrated than for incident ones, (15%, 76%, 7% and 2% compared to 9%, 83%, 8% and 0%, respectively for abacavir/lamivudine; tenofovir/emtricitabine; zidovudine/lamivudine and tenofovir/lamivudine).

	Patient (n.)
Residents	60,626,442
Prevalent HIV patients	61,175
No virologic failure patients	43,373
Excluded for regimen	4,338
Annual target population	**39,035**

Table X. *Flow for prevalent patients analysis*

Regimens	Prescriptions (n.)	
	Current scenario	Base case hypothetical scenario
ABC/3TC/RAL	102	256
ABC/3TC/DRV/r	411	1.351
ABC/3TC/ATV/r	2,244	3.429
ABC/3TC/LPV/r	810	2.154
ABC/3TC/EFV	903	5.190
ABC/3TC/NVP	791	1.642
ABC/3TC/fAPV/r	493	654
TDF/FTC/RAL	560	364
TDF/FTC/DRV/r	3,118	1.920
TDF/FTC/ATV/r	6,624	4.874
TDF/FTC/LPV/r	3,628	3.062
TDF/FTC/EFV	12,470	7.376
TDF/FTC/NVP	2,287	2.334
TDF/FTC/fAPV/r	1,096	930
AZT/3TC/RAL	19	50
AZT/3TC/DRV/r	31	262
AZT/3TC/ATV/r	126	666
AZT/3TC/LPV/r	1,107	418
AZT/3TC/EFV	302	1.008
AZT/3TC/NVP	1,157	319
AZT/3TC/fAPV/r	107	127
TDF/3TC/RAL	0	11
TDF/3TC/DRV/r	32	60
TDF/3TC/ATV/r	127	151
TDF/3TC/LPV/r	184	95
TDF/3TC/EFV	127	229
TDF/3TC/NVP	134	73
TDF/3TC/fAPV/r	44	29

Table XI. *Prevalent patients distribution among considered regimens*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir
* Of which 85% receive co-formulation Atripla®

Cost results

Table XII presents annual cost for each considered regimen, divided into pharmaceutical, preventive and monitoring expenses, listed in ascending order of total cost. Pharmaceutical cost represents the most important cost item and is responsible of the major cost difference among regimens; monitoring expenses vary in

Regimens	Pharmaceutical costs (€)		Preventive exams (€)	Monitoring investigations (€)	Total cost (€)	
	Backbone	Third drug			Year 1	Following years
AZT/3TC/NVP	3,814.25	2,288.55		68.87	6,171.67	6,171.67
AZT/3TC/EFV	3,814.25	2,609.75		68.87	6,492.87	6,492.87
TDF/3TC/NVP	4,420.52	2,288.55		163.10	6,872.17	6,872.17
TDF/3TC/EFV	4,420.52	2,609.75		163.10	7,193.37	7,193.37
ABC/3TC/NVP	4,846.11	2,288.55	56.23	77.66	7,268.55	7,212.32
ABC/3TC/EFV	4,846.11	2,609.75	56.23	77.66	7,589.75	7,533.52
TDF/FTC/NVP	5,339.95	2,288.55		163.10	7,791.60	7,791.60
TDF/FTC/EFV	5,339.95	2,609.75		163.10	8,112.80	8,112.80
Co-form. TDF/FTC/EFV	5,299.80	2,649.90		163.10	8,112.80	8,112.80
AZT/3TC/LPV/r	3,814.25	4,352.26		100.73	8,267.24	8,267.24
AZT/3TC/ATV/r	3,814.25	4,354.09		108.35	8,276.69	8,276.69
AZT/3TC/fAPV/r	3,814.25	4,452.27		86.45	8,352.97	8,352.97
AZT/3TC/DRV/r	3,814.25	4,542.79		86.45	8,443.49	8,443.49
TDF/3TC/LPV/r	4,420.52	4,352.26		180.68	8,953.46	8,953.46
TDF/3TC/ATV/r	4,420.52	4,354.09		188.30	8,962.91	8,962.91
TDF/3TC/fAPV/r	4,420.52	4,452.27		180.68	9,053.47	9,053.47
TDF/3TC/DRV/r	4,420.52	4,542.79		180.68	9,143.99	9,143.99
ABC/3TC/LPV/r	4,846.11	4,352.26	56.23	100.73	9,355.33	9,299.10
ABC/3TC/ATV/r	4,846.11	4,354.09	56.23	108.35	9,364.78	9,308.55
ABC/3TC/fAPV/r	4,846.11	4,452.27	56.23	86.45	9,441.06	9,384.83
ABC/3TC/DRV/r	4,846.11	4,542.79	56.23	86.45	9,531.58	9,475.35
TDF/FTC/LPV/r	5,339.95	4,352.26		180.68	9,872.89	9,872.89
TDF/FTC/ATV/r	5,339.95	4,354.09		188.30	9,882.34	9,882.34
TDF/FTC/fAPV/r	5,339.95	4,452.27		180.68	9,972.90	9,972.90
TDF/FTC/DRV/r	5,339.95	4,542.79		180.68	10,063.42	10,063.42
AZT/3TC/RAL	3,814.25	6,343.70		68.87	10,226.82	10,226.82
TDF/3TC/RAL	4,420.52	6,343.70		163.10	10,927.32	10,927.32
ABC/3TC/RAL	4,846.11	6,343.70	56.23	77.66	11,323.70	11,267.47
TDF/FTC/RAL	5,339.95	6,343.70		163.10	11,846.75	11,846.75

Table XII. *Annual cost for regimen; strategies are listed in ascending order of total cost*
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; DRV = darunavir; EFV = efavirenz; fAPV = fosamprenavir; FTC = emtricitabine; LPV = lopinavir; NVP = nevirapine; r = ritonavir; RAL = raltegravir; TDF = tenofovir

a narrow range (from 69 euro for zidovudine/lamivudine/efavirenz to 188 euro for tenofovir/emtricitabine/atazanavir), whereas preventive cost is applied only to abacavir-based regimens. As shown in the Table, NNRTI-based regimens are cheapest; among these, the rank of the backbones in ascending order of annual cost corresponds to zidovudine/lamivudine, tenofovir/lamivudine, abacavir/lamivudine, and tenofovir/emtricitabine. The lower monitoring cost of abacavir-based regimens (ranging between 78 and 108 euro according to the third drug) with respect to tenofovir/emtricitabine ones (ranging between 163 and 188 euro) is partly offset by their preventive costs (€ 56). The remaining monitoring cost saving, added to the averagely lower pharmaceutical cost (for backbone € 4,846 vs € 5,340) is the net saving estimate, linked to the use of abacavir/lamivudine compared to the other first choice backbone. For the first year of therapy the total cost of these two strategies ranges between 7,269 and 11,324 euro for abacavir/lamivudine and between 7,792 and 11,847 euro for tenofovir/emtricitabine; the difference slightly increases in following years because of the absence of preventive cost.

		Current scenario	Base case hypothetical scenario
Patients (n.)		15,703	15,703
Backbone cost (€)		81,110,391	78,941,216
Third drug cost (€)		59,465,733	59,414,689
Complete regimen cost (€)		140,576,123	138,355,905
Preventive exams cost (€)		46,508	194,952
Monitoring investigations (€)		2,542,719	2,152,115
Total cost (€)		**143,165,351**	**140,702,973**
Budget impact H vs C	**(€)**	**-2.462.379**	
	(%)	**-1.7**	

Table XIII. *Incident patients analysis three years-cumulative Budget Impact results*

		Current scenario	Base case hypothetical scenario	Budget Impact H vs C	
				€	%
Year 1	Patients (n.)	3,074	3.074	**-461,546**	**-1.65**
	Total cost (€)	28,028,743	27,567,197		
Year 2	Patients (n.)	5,355	5,355	**-840,805**	**-1.72**
	Total cost (€)	48,818,790	47,977,986		
Year 3	Patients (n.)	7,275	7,275	**-1,160,028**	**-1.75**
	Total cost (€)	66,317,818	65,157,790		

Table XIV. *Incident patients analysis single year Budget Impact results*

Budget impact

Table XIII shows the financial impact that Italian National Health Service may expect if for the next three-year period patients starting HAART were treated according to the base case hypothetical scenario. The prescriptions switch from tenofovir/emtricitabine to abacavir/lamivudine for a portion of new patients for which this regimen represents a first choice treatment (HLA-B*5701 allele negative and viral load < 100,000 copies) induces a cost saving, mainly due to the lower acquisition cost, of almost 2.5 million euro. The total cost for preventive exams is, obviously, slightly higher in the hypothetical scenario, since only abacavir hypersensitivity test is considered in the analysis, whereas monitoring expenses are about 400 thousand euro higher in the current setting.

As shown in Tabel XIV, where BIM results are reported for each single year, savings grow with increasing numerousness of the target pool; the same holds true in regional contexts: Lombardia presents highest cost saving; at the opposite Valle d'Aosta, with its cumulative 46 patients (data not shown).

For the simulation running on the prevalent population, the considerations that can be drawn are similar: the increase, in the past years, of abacavir/lamivudine market shares could now induce a net annual cost saving of more than 5 million euro (Table XV). Table XVI shows how results change according to the variability of tested prescriptions modification: the minimum scenario forecasts that only 20% of patients present low viral loads; in the maximum one this portion is increased to 50%. Budget Impact related to incident patients varies between a saving of 850 thousand euro and of 3.3 million euro, respectively for minimum and maximum scenario. For prevalent patients these figures are equal to 922 thousand euro and 7.3 million euro.

		Current scenario	Base case hypothetical scenario
Patients (n.)		39,035	39,035
Backbone cost (€)		200,232,519	195,999,766
Third drug cost (€)		139,480,733	139,306,748
Complete regimen cost (€)		339,713,253	335,306,513
Monitoring investigations (€)		6.057.094	5,296,737
Total cost (€)		**345.770.346**	**340,603,250**
Budget impact H vs C	**(€)**	**-5,167,096**	
	(%)	**-1.5%**	

Table XV. *Prevalent patients analysis annual Budget Impact results*

DISCUSSION AND CONCLUSIONS

Since the advent of triple therapy in the mid-1990s, the clinical course of HIV infection is changed, reducing the disease progression, the mortality and the incidence of opportunistic infections: HIV patients, fortunately, live longer and better, especially in developed countries.

	Current scenario	Minimum hypothetical scenario	BI H vs C	Maximum hypothetical scenario	BI H vs C
3-year incident patients					
Patients receiving ABC/3TC (n.)	1,409	2,952	+1,543	7,380	+5,971
Total cost (€)	143,165,351	142,315,350	-850,001	139,896,784	-3,268,568
Prevalent patients					
Patients receiving ABC/3TC (n.)	5,754	7,339	+1,585	18,346	+12,592
Total cost (€)	345,770,346	344,847,853	-922,493	338,480,949	-7,289,398

Table XVI. *Incident and prevalent patients analyses running on minimum and maximum hypothetical scenarios*
ABC = abacavir; C = current; H = hypothetical; 3TC = lamivudine

Italian [1] and international guidelines [17,21] state that HAART is indicated for all HIV individuals, with strong recommendation for those with a CD4 count <500 cells/mm^3. In general, this leads to a very large pool of patients receiving treatment and to a consequent high overall expenditure. For many national health care services, especially in the case of contemporary reduction in health care funding as it happens in Italy, this may not be affordable. Furthermore, other issues regarding patient management have recently changed; for example new guidelines recommend PEGylated interferon or ribavirin for the treatment of HCV co-infection [17] and new expensive drugs, such as raltegravir, darunavir, etravirine, maraviroc, have begun to spread; as a results, the cost of HIV care is bound to further increase. Rizzardini and colleagues conducted a retrospective, observational, longitudinal study, involving 483 patients followed at the First Infectious Disease Department of "L Sacco" Hospital in Milan (Lombardia-Italy) in 2007–2009 [22]. Despite the improvement of the mean CD4+ cell count over the study period, the total cost increased by 5% in 2008 and by 25% in 2009. This was mainly due to the increase of the frequency of hospital admission and of the prevalence of use of expensive regimens based on raltegravir, darunavir, etravirine, or maraviroc (means total cost € 18,490 vs. 11,100 for patients not prescribed new drugs). Even if the cost for non-HIV drugs and for outpatient visits slightly decreased, this trend appears not sufficient to offset the increase in other expenditure items.

This study underlines that to achieve immunological improvement, founding has to be augmented, at least in the short term. The resulting economic burden induces health care providers to increasingly focus their attention on the crucial union between cost and the appropriateness of care. In terms of cost, the annual mean HAART cost (€ 8,952) estimated by our model is quite consistent with that emerged from the study by Rizzardini et al. (€ 8,471). Since the pharmaceutical costs are taken from the same data source (Hospital "Sacco" in Milan), this consistence shows a comparable distribution of patients among strategies with different economic burden. Instead, the total cost estimated by Rizzardini et al. is higher than the value here found (€ 9,117 vs. 11,735), since it comprised also hospital admission and outpatient visits, whereas in the present analysis the routine clinical management of the patient is not considered, aiming to focus on differential and regimen-dependent costs only.

Compared to our model-estimated mean HAART cost (€ 8,952), 5 out of seven abacavir/lamivudine (€ 7,135-11,190) and tenofovir/emtricitabine (€ 7,629-11,684) based strategies are more expensive that this value, whereas for tenofovir/lamivudine (€ 6,709 - 10,764) and for zidovudine/lamivudine (€ 6,103 - 10,158) this figure decreases to 2 and 1, respectively. Despite the growing need for health care resources rationalization, these cheaper backbones are the least prescribed ones in Italy, with market share lower than 2% for zidovudine/lamivudine and of about 7-8% for the other one.

In order to explain this apparently irrational condition it's necessary to draw the attention on the other term of the earlier mentioned crucial union: the appropriateness of care. Zidovudine/lamivudine-based regimens are recommended by the guideline only as an alternative choice, for lower effectiveness, worse toxicity profile, and minor genetic barrier. On the other hand, tenofovir and lamivudine are not available in co-formulation, whereas guidelines strongly prompt for lower pill burden regimens.

Restricting the comparison to the only two backbones recommended as first choice, our model estimates a lower cost for abacavir/lamivudine compared to tenofovir/emtricitabine; this leads to a potential cost saving of almost 2,5 million euro for incident patients over a cumulative three-year period and more than 5 million euro for the almost 40 thousand prevalent patients, against a drastic increase of its market share. This potential result strongly depends on the number of patients that hypothetically switches from tenofovir/emtricitabine to abacavir/lamivudine and this value represents an uncertain parameter, influenced by many factors, also linked to prescription habits and individual experiences. In order to assess the impact of this uncertainty in our analysis, we provided minimum and maximum settings, estimating a potential cost saving ranging, for incident patients, between 850 thousand and 3,3 million euro, for the share of patients receiving abacavir/lamivudine moving from 19% to 47% of the total market. However, to turn this potential saving into something real, in order to create the conditions for the National Health Service to reallocate efficiently the resources, it's important that abacavir/lamivudine represents an appropriate choice of treatment, and not only a convenient option, especially with respect to tenofovir/emtricitabine.

During the last years, increasing attention has been given to "complementary" factors, besides the "traditional" effectiveness, measured by lymphocyte count or viral load. Accepta-

ble long-term safety profiles, minimal management requirements (thermostability and low pill burden) and safety in pregnant women are now main key issues, under equal effectiveness assumption. For the second item, for example, tenofovir/emtricitabine presents the advantage to be available, with efavirenz, in a unique tablet formulation. It's considered the gold standard for a good portion of the scientific community; however not every patient may receive this regimen: efavirenz in currently not recommended for use in pregnancy, and some safety concerns referring to tenofovir are under an active debate.

Two trials found greater decreases in bone mineral density (BMD) with tenofovir/emtricitabine than with abacavir/lamivudine-based treatment [23,24]. To date, only one trial recorded BMD data among virologically suppressed HIV patients [25] and its results highlighted significant reductions in hip and spine BMD. However, the clinical significance of these differences remains uncertain, as they were not correlated to more fractures. For renal complications onset, another relevant safety concern, this trial reported no significant between-group difference for glomerular filtration rate and other common parameters. On the contrary, a recent meta-analysis comparing tenofovir-containing with tenofovir not-containing regimens shows a small but statistically significant loss of renal function associated to tenofovir [26]. Also abacavir/lamivudine is not immune from safety troubles; the association between abacavir administration and myocardial infarction (MI) has been heavily debated. Briefly, this association has been found in two cohort studies [27,28]; whereas data from the AIDS Clinical Trial Group [29] on naïve patients, short and long-term results from ACTG A5001 [30], the Veterans Health Administration's Clinical Case Registry [31], and a study conducted on the HIV French Hospital Database with the case-control methodology [32] did not find a significant causal relationship between abacavir and MI. In randomized controlled trials comparing ABC with tenofovir, no increase in MI rate has been detected [2-4]. Only the STEAL-study, in which patients assigned to the abacavir treatment had higher prevalence of cardiovascular risk factors, detected an increased rate of cardiovascular events with the use of this drug [25]. A two recent meta-analysis of randomized trials have almost definitively clarified that no association between MI and abacavir exists [33,34].

The cost saving estimated is conservative since the impact of co-morbidities is entered in the model only as cost of monitoring examinations to prevent/evaluate these conditions, not also as side effect management expenditure. Furthermore, only abacavir-related preventive test is considered among cost items. Other possible preventive exams, like the renal function evaluation before starting tenofovir-based therapies, the investigation of mutations on binding site between raltegravir and integrase-enzyme, psychiatric illness anamnesis in case of efavirenz use are recommended by guidelines. We excluded these costs from the modeling because of their poor adoption in the real clinical practice.

Some limitations of the presented analysis are related to the epidemiologic data; the estimated prevalence of HIV patients is lower than that usually found in registries/databases, probably due to the selected target: our model is fed only with treated patients, whereas in the epidemiologic source, generally, the number of all prevalent patients is reported. An assumed compliance of 100% may underestimate our pool of patients, identified on basis of drug prescriptions; on the other hand, it was not possible to separate drug sales allocated to hepatitis care from those for HIV treatment and this may produce an overestimate of the cohort. Furthermore, for practical reasons, patients receiving heroic or not-recommended regimens based on resistance test have been excluded from the analysis, despite their use in real clinical practice. These limitations notwithstanding, our model results indicate that the evaluated change in prescription pattern, increasing abacavir/lamivudine market share at the expense of other backbones, represents a choice of convenience and appropriateness. It makes the objective to guarantee the administration of an equally effective and equally or more safe regimen to naive patients possible, with a resources release that may be dedicated to more severe/multi-resistant/problematic patients.

REFERENCES

1. LG 2012. Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1, July 2012, with the approval of the Ministry of Health. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1793_allegato.pdf

2. Martínez E, Arranz JA, Podzamczer D, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in hiv-1-infected patients with virological suppression. *J Acquir Immune Defic Syndr* 2009; 51: 290-7; http://dx.doi.org/10.1097/QAI.0b013e3181aa12d5

3. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinair/ritonavir for initial HIV treatment. *AIDS* 2009; 23: 1547-56

4. Sax PE, Tierney C, Collier AC, et al. Abacavir–Lamivudine versus Tenofovir–Emtricitabine for Initial HIV-1 Therapy. *N Engl J Med* 2009; 361: 2230-40; http://dx.doi.org/10.1056/NEJMoa0906768

5. Mauskopf JA, Sullivan SD, Annemans L, et al. Principles of Good Practice for Budget Impact Analysis: Report of the ISPOR Task Force on Good Research Practices - Budget Impact Analysis. *Value in health* 2007; 5: 33647; http://dx.doi.org/10.1111/j.1524-4733.2007.00187.x

6. ISS 2011. Notiziario dell'Istituto Superiore di Sanità 2011; 24 Suppl. 1. Last update December 2009

7. IMFO 2011-2012. Source IMS. Year 2012. ViiV Health Care - data on file

8. Murray M, Hogg R, Lima V, et al. The effect of injecting drug use history on disease progression and death among HIV-positive individuals initiating combination antiretroviral therapy: collaborative cohort analysis. *HIV Med* 2011

9. Colombo GL, Colangeli V, Di Bigagio A, et al. Cost-effectiveness analysis of initial HIV treatment under Italian guidelines. *ClinicoEconomics and Outcomes Research* 2011: 3; 197-205; http://dx.doi.org/10.2147/CEOR.S24130

10. Istat 2011. Available at www.demo.istat.it (last accessed April 2012)

11. Merito M, Bonaccorsi A, Pammolli F, et al. Valutazione economica dei trattamenti anti-HIV: lo studio di coorte I.CO.N.A. *Giornale italiano di malattie infettive* 2004; 3

12. Krishnan S, Schouten JT, Atkinson B, et al. Metabolic syndrome before and after initiation of antiretroviral therapy in treatment-naïve HIV-infected individuals. *Journal of Acquired Immune Deficiency Syndromes* 2012; 61: 381-9;. http://dx.doi.org/10.1097/QAI.0b013e3182690e3c

13. Buskin SE, Zhang S, Thibault CS. Prevalence of and Viral Outcomes Associated with Primary HIV-1 Drug Resistance. *The Open AIDS Journal* 2012; 6 (Suppl 1: M17): 181-7

14. Franzetti M, Violin M, Casazza G, et al. Human immunodeficiency virus-1 B and non-B subtypes with the same drug resistance pattern respond similarly to antiretroviral therapy. Clin *Microbiol Infect* 2012; 18: E66-E70; http://dx.doi.org/10.1111/j.1469-0691.2011.03740.x

15. Prosperi MCF, Di Giambenedetto S, Fanti I, et al. A prognostic model for estimating the time to Vvirologic failure in HIV-1 infected patients undergoing a new combination antiretroviral therapy regimen. *BMC Medical Informatics and Decision Making* 2011; 11: 1-9

16. Orkin C, Wangb J, Berginc C, et al. An epidemiologic study to determine the prevalence of the HLA-B*5701 allele among HIV-positive patients in Europe. *Pharmacogenetics and Genomics* 2010; 20: 307-14; http://dx.doi.org/10.1097/FPC.0b013e3283390666

17. AIDSinfo.nih.gov. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2008. Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (last accessed April 2012)

18. PDT 2012. Update of "Percorso diagnostico-terapeutico del paziente affetto da malattia HIV-AIDS" D.D.G. 3546 del 23/4/2012. Regione Lombardia

19. IF 2012- Informatore farmaceutico. May 2012. Available at www.Codifa.it

20. NomSpec 2009. Agenzia Nazionale per i Servizi Sanitari Regionali. Tariffe delle prestazioni specialistiche ambulatoriali. Updated to 31 December 2009. Available at: www.agenas.it/monitoraggio_costi_tariffe/2009_SPECIALISTICA_ex%20DM%2096per%20sito.pdf (last accessed April 2012)

21. EACS - European AIDS Clinical Society Guidelines. October, 2011. Available at: http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf (last accessed April 2012)

22. Rizzardini G, Restelli U, Bonfanti P, et al. Cost of human immunodeficiency virus infection in Italy, 2007-2009: effective and expensive, are the new drugs worthwhile? *Clinicoecon Outcomes Res* 2012; 4: 245-52; http://dx.doi.org/10.2147/CEOR.S35194

23. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010; 51: 963-72; http://dx.doi.org/10.1086/656417

24. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: aids clinical trials group A5224s, a substudy of ACTG A5202. *J Infect Dis* 2011; 203: 1791-801; http://dx.doi.org/10.1093/infdis/jir188

25. Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. *Clin Infect Dis* 2009; 49: 1591-601; http://dx.doi.org/10.1086/644769

26. Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIVinfected patients. *Clin Infect Dis* 2010; 51: 496-505; http://dx.doi.org/10.1086/655681

27. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008, 371: 1417-26; http://dx.doi.org/10.1016/S0140-6736(08)60423-7

28. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIVinfected patients on highly active antiretroviral therapy: a populationbased nationwide cohort study. *HIVMed* 2010, 11: 130-6; http://dx.doi.org/10.1111/j.1468-1293.2009.00751.x

29. Brothers CH, Hernandez JE, Cutrell AG, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr* 2009; 51: 20-8; http://dx.doi.org/10.1097/QAI.0b013e31819ff0e6

30. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis* 2011; 52: 929-40; http://dx.doi.org/10.1093/cid/ciq244

31. Bedimo RJ, Westfall AO, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. *Clin Infect Dis* 2011, 53: 84-91; http://dx.doi.org/10.1093/cid/cir269

32. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med* 2010; 170: 1228-38; http://dx.doi.org/10.1001/archinternmed.2010.197

33. Ding XA-CE, Cooper C, Miele P, et al. No Association of Myocardial Infarction with Abacavir Use. 18th Conference on Retroviruses and Opportunistic Infections Boston; 2011, Abstract # O-1004

34. Cruciani M, Zanichelli V, Serpelloni G, et al. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. *AIDS* 2011, 25: 1993-2004

