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InforMatrix Nucleoside/Nucleotide Reverse Transcriptase Inhibitors "Backbones"

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1. Introduction

InforMatrix is an interactive matrix model, in which pharmacotherapeutic strategies are supported in a rational manner by means of a transparent selection methodology. This is achieved through the use of an independent reporting made by interactive workshops in the field, in which participants are facilitated in the determination of their own preference.
The treatment of AIDS is directed by guidelines and continually being modified as a result of ongoing research and the arrival of new treatment options. The goal of this InforMatrix program on backbones of nucleoside/nucleotide reverse transcriptase inhibitors is to make a rational selection of a first choice medication possible. It is important in this to describe the selection process and to make this process transparent. The InforMatrix methodology is a tool in this, in which selection criteria are described; tested against the available literature and the various therapeutic alternatives evaluated as to their clinical value.
Below follows a short description of the InforMatrix methodology, of the subject, and a description of the various selection criteria.

1.1 InforMatrix methodology

InforMatrix is a so-called decision matrix technique, with which a group of experts in the subject determine, on the basis of criteria, an order of merit within various treatment options which have similar objectives. In this order of merit, the criteria are weighed against each other. After all, they do not all carry the same weight. Next, the various options per criterion are compared to each other. Data is necessary for this, both from literature as well as from own practice experience. The literature is tested by an independent ethisor for clinical value and evaluated per criterion.
The InforMatrix technique has six set criteria. These criteria are:

- *Effectiveness* (the actualization of positive outcomes and treatment goas)
- *Safety* (the avoidance of negative outcomes, such as hazardous side effects)
- *Tolerance* (the interruption of the care process due to less hazardous, generally transitory, but disturbing side effects)
- *Users' ease* (ease for the patient, for example, dosing frequency)
- *Usability* (what is the scope of the treatment freedom (interactions and such) and the ease for the caregiver)
- *Costs* (price per month)

These criteria are specifically described per selection subject ("operationalized").
The InforMatrix technique takes place in the following steps:

- Operationalization of the six criteria
- Literature synthesis
- Relative weighing of the six criteria
- Evaluation of the various treatment options on the basis of the literature and own knowledge and experience
- Synthesis of the weightings and evaluations in the selection matrix: calculation of order of merit

A group of experts in the field are requested to test the operationalization of the above six selection criteria in the framework of the treatment of HIV/AIDS in the care process for relevance. Following on to these selection aspects, the authors execute a literature synthesis. This results in a report, in which these means are evaluated on the basis of these selection criteria by a group of experts in the field. In this, the report is tested as far as its applicability in making a rational consideration of the treatment options possible.
The choice of nucleoside/nuclotide reverse transcriptase inhibitors and the assessment criteria
After the introduction of nucleoside/nuclotide reverse transcriptase inhibitors (NRTIs), the first antiretroviral drugs approved for the treatment of HIV, patients were initially treated with one drug (monotherapy) and later with two NRTIs (duotherapy). After the introduction of protease inhibitors effective treatment of the HIV infection was possible. This so called HAART (highly active antiretroviral therapy) initially consisted of a combination of 2NRTIs with a proteaseinhibitor (PI).
New classes of antiretrovirals have been developed and nowadays many more combinations of antiretrovirals are possible. A backbone therapy consisting of 2NRTIs in combination with a third drugs like a PI, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an integrase inhibitor is still chosen as an initial combination antiretroviral therapy (cART).
The treatment goal of cART is to attain an undetectable plasma viral HIV-1 load (VL), after which a recovery of immunity usually follows.
In a meta-analysis covering 64 clinical trials with in total 10,559 naive patients HAART consisting of 2NRTI/PI/ritonavir or 2NRTI/NNRTI both produce significantly higher percentages of patients with undetectable VL and a significantly higher increase of CD4 positive T-lymphocytescount (CD4 cell count) than cART consisting of 2NRTI/PI or 3NRTI **(1).**
Although stavudine (d4T) is a effective anti-retroviral drug, especially in combination with didanosine, its use is no longer recommended because of the increased change for the development of lipoatrophy during treatment and high rates of mitochondrial toxicity **(2).**
Combining ddI with tenofovir leads to a specific renal interaction causing high drug levels of didanosine and ddI toxicity resulting in decrease of CD4 cell count **(3)**. Lowering of ddI dosing leads to an increased change of developing virological failure **(4)**.
The following combinations are compared in this InforMatrix because they are recommended in the three major guidelines, the American DHHS Panel (December, 2009) **(5),** the European AIDS Clinical Society (November, 2009) **(6)** and the International AIDS Society-USA Panel **(7)**

a. Abacavir/lamivudine (fixed dose combination Kivexa® or Epzicom®) abbreviated as ABC/3TC

b. Didanosine/lamivudine or emtricitabine abbreviated as ddI/3TC or FTC
c. Tenofovir/emtricitabine (fixed dose combination Truvada®) abbreviated as TDF/FTC
d. Zidovudine/eamivudine (fixed dose combination Combivir®) abbreviated as ZVD/3TC

The following criteria and subcriteria were used:

1. Efficacy of anti-retroviral backbones
   1.1 Parameters of efficacy of anti-retroviral backbones
   1.2 Compliance, quality of life and durability of anti-retroviral backbones
   1.3 Development of resistance during treatment with anti-retroviral backbones
2. Safety of anti-retroviral backbones
   1.4 Grade 3 and 4, serious adverse events
   1.5 Documentation
3. Tolerability of anti-retroviral backbones
   1.6 Grade 1 and 2, mild to moderate adverse events
4. Easy of use
   1.7 Dosage frequency, number of tablets per day
5. Applicability
   1.8 Available strengths
   1.9 Drug interactions
   1.10 Approved indications
   1.11 Contra-indications
   1.12 Use in children and elderly
   1.13 Use in renal and hepatic disease
   1.14 Use in pregancy and lactation
   1.15 Special precautions
6. Cost

2. Efficacy of anti-retroviral backbones

2.1 Parameters of efficacy of anti-retroviral backbones

The efficacy of a cART, usually consisting of 2NRTIs in combination with a PI or NNRTI is judged by the results of its anti-retroviral efficacy, increase of CD4 cell count and change of developing resistance.

The combination of 3 NRTIs as initial therapy is no longer used since the availability of the results of the ACTG 5095 study **(8)**. Limited data are available on combinations of one NRTI + NNRTI+PI the so called NUC-sparing regimen or other combinations. In has been shown in meta-analyses that HAART consisting of 2NRTIs + PI, not combined with ritonavir (as a booster) is virologically and immunologically less effective than 2NRTIs+NNRTI or 2NRTIs + PI combined with ritonavir **(1).**

The anti-retroviral efficacy of cART must lead to undetectable VL, less than 50 copies/mL (VL<50 c/mL), in older studies a pVL < 400 c/mL is used as measure of undetectability.

If the VL does not become undetectable this almost always leads to the development of resistance and to antiviral inefficacy of a certain drug or a whole class of drugs resulting in a decrease of the CD4 cells. This ongoing decrease in the number of CD4 cells leads to HIV related diseases, AIDS and death. The antiviral efficacy is one of the most important parameter for the efficacy of a certain regimen. Te so called "regimen failure" which is a

broader measure effectivity of an antiretroviral regimen includes not only virological failure but all other reaons for stopping a regimen such as adverse effects or death and indicates its clinical efficacy.

Studies in patients who are not pretreated (naive patients) and harbouring no significant resistant mutations provide the best indication of the antiviral and clinical efficacy.

The percentage of naive patients in a certain study after 48 weeks, but preferably longer, in the intent to treat analysis (ITT) showing a VL<50 c/mL, is regarded as the best parameter for clinical efficacy. Often missing data on participants (M) are considered as virologic failures (F) (ITT analysis M=F) **(5).**

Increase of CD4 cell count is of less importance as a parameter of efficacy, because an undetectable VL almost always leads to recovery of CD4 cell count and the mean increase in CD4 cell count is probably similar in the different strata of CD4 cell count when starting cART. For instance in the Athena Dutch cohort study the average increase in CD4 cell count after initiation of therapy was around 70 cells/mm^3 per year during seven years of continuous cART with an undetectable VL. In the first six months after start of cART the increase was on average around 140 cells/mm^3 . Patients starting cART when the CD4 cell count was above 500 cells/mm^3 had on average a lower increase CD4 cell of around 40 cells/mm^3 per year **(9).**

There are seven major randomized studies **(10-17**) comparing backbones combined with a similar third drug. The results of these comparative studies are summarised in Table 1.

In the three above mentioned guidelines two **(3,5**) recommend to start with TDF/FTC and ABC/3TC as an alternative to start with.

-In the HEAT **(10)** and ACTG 5202 **(11,12)** these two fixed dose combinations were compared with each other. In the HEAT study the third drug was a PI, lopinavir/ritonavir and in the ACTG 5202 it was a NNRTI, efavirenz or a PI, atazanavir/ritonavir. The HEAT study is an industry sponsered study.

ABC is known for its hypersensitivity reaction usually appearing in the first six week after starting ABC therapy. This hypersensitivity can lead to serious complications and death if not recognized. The presence of HLA-B5701 antigen is highly predictive for the chance of developing this hypersensitivity reaction **(18).**

In boths studies no determination for the presence of HLA-B5701 antigen was done.

In the HEAT study **(10)** the effectivity and CD4 cell count increase of both regimens after 48 weeks of treatment and safety after 96 weeks of treatmet was similar. In both treatment arms 2% of the participants had a grade 3-4 **(19)** decrease in renal function.

Of importance in this study is the fact that there was no difference in anti-vial efficacy between both treatment arms for participants with a high screening VL greater than 100,000 copies/ml (high VL). In the ACTG 5202 the anti-viral efficacy of the regimens were similar for participants with a screening VL less than 100,000 copies/ml **(12)** but not for those participants with a high screening VL. In the ACTG 5202, 43% of the participants had a high screening VL **(11).** At a median follow-up of 60 weeks, among the 797 patients with high VL, the time to virologic failure was significantly shorter in the ABC/3TC group than in the TDF/FTC group. There were 57 virologic failures (14%) in the ABC/3TC group versus 26 (7%) in the TDF/FTC group. The time to the first adverse event was also significantly shorter in the ABC/3TC arm. The increase in CD4 cells from baseline at week 48 was similar.

In an analysis of five pharmaceutical company sponsored trials with 872 paticipants with high sreening VL treated with ABC/3TC and using the same criteria for virological

failure as in the ACTG 5202 study there was no inceased chance for virological failure in this group **(20).**
But in a meta-analysis of 12 trials with 4896 participants and also using the same criteria for virological failure as in the ACTG 5202 study TDF/FTC showed to be virological more effective than ABC/3TC **(21).**
-In a number of trials **(13-17**) (see table 1) combination regimens with ZVD or combination regimens with d4T are less effective or result in a lower increase of CD4 cell count than in the comparative study arm.
For instance in two trials comparing ABC/3TC with ZVD/3TC **(14)** and TDF/FTC with ZVD/3TC **(13)** a significant lower increase in CD4 count is seen in both ZVD/3TC study arms than in the comparative study arms. In the 934 study **(13)** significant differences were seen in the proportion of patients with VL less than 50 copies/ml (80% versus 70%). Significant more patients in de ZVD/3TC arm had virologic failure, 4% versus <1% in the TDF arm.
More patients in theZVD/3TC group than in the TDF/FTC group had adverse events resulting in discontinuation of the study drugs **(13**). These adverse events were mainly anemia, nausea, vomiting and fatigue. The authors concluded that through week 48, TDF/FTC proved to be superior in terms of virologic suppression, CD4 response and adverse events resulting in discontinuation of the study drugs.
Also in other studies, serious adverse events like anemia and leukopenia are seen in patients taking ZVD and are often a reason for stopping ZVD **(14, 15).**

2.2 Compliance, quality of life and durability of anti-retroviral backbones

Good compliance is the cornerstone for succes of anti-retroviral therapy. Stress reduction, a good sociaal network and adequate information play an important role **(22).** Irregular intake of medication by inadequate compliance leads to suboptimal plasma levels of the medication, thereby increasing development of resistance (**23, 24**) Compliance which leads to actual intake of > 95% of the prescribed medication is a predictor of efficacy of a regimen **(23,24)**.
Adverse events, the number of pills and dosage frequency determine compliance.
In different meta-analyses of 64 **(25)** and 20 **(26)** clinical trials it was shown that the number of tablets per day, dosage fequency and diet restrictions (with food or on an empty stomach) are important determinants of success of antiretroviral therapy. In the meta-analysis of 64 clinical trials **(25**) the number of tablets per day was the most important factor for success of cART.
A meta-analysis of 11 randomized trials revealed that the adherence rate was better with once-daily regimens than twice-daily regimens and this effect was more pronounced at the time of treatment initiation **(27).**
No studies on quality of life (QoL) and compliance have been done linked to the seven major randomized studies mentioned above.
In a meta analysis, initial ART regimens, regimens containing TDF are equivalent to those containing AZT concerning serious adverse events. However, TDF showed to be superior to AZT in terms of immunologic response and adherence and less frequent emergence of resistance **(28).**
In a review of twenty-two randomized controlled trials including all above mentioned backbones, including 8,184 HIV-treatment-naïve patients, the combination ddI/3TC was anti-virologic more effective and less toxic for discontinuation due to adverse events and more tolerable than its comparators. The combination TDF/3TC or FTC was more effective

and less toxic only in the 144-week follow-up data (two trials, 1,119 patients). ABC/3TC had similar efficacy to its comparators, but more AIDS-defining events **(29**). In the Swiss cohort study, including 1318 naïve patients, between 2005 and 2008 drug toxicity remained a frequent reason for treatment modification. Initial treatment with ZVD/3TC was associated with a high rate of drug toxicity. **(30)** In general QoL is beter with a higher CD4 cell count and QoL is decreased in patients with a high VL. The effects of adverse events on QoL are independent of CD4 cell count and VL **(31).**

Acronime of study	Set up of study	Treatment arms Number of patients in each treatment arm ()	Third drug	ITT analysis: % patients with VL< 50 cop/mL	% patients with screening VL >100.000 copies/mL with VL< 50 copies/mL	CD4 increase cells/mm^3	% patients stopping study drugs due to adverse events
HEAT Sudy #(10)	randomised dubble blind placebo controlled	ABC/3TC (343) versus TDF/FTC (345)	lopinavir/r	68% vs 67%	63% vs 65%	214 vs 193	up to week 96: 6% vs 6%
ACTG 5202# (11,12)	randomised blinded for backbone	ABC/3TC (388) versus TDF/FTC (393)	atazanavir/r or efavirenz	similar	75% vs 80%	194 vs 199	up to week 112: 5% vs 4%
Gilead 934 Study (13)	randomised open label	TDF/FTC(258) versus ZVD/3TC (259)	efavirenz	77% vs 68%**	not available	190 vs 158*	up to week 48: 5% vs 19%* up to week 144: 13% vs 34%*
CNA30024# (14)	randomised dubble blind	ABC/3TC (327) versus ZVD/3TC (327)	efavirenz	70% vs 69%	67% vs 67%	209 vs 155**	up to week 48: 14% vs 18%
GESIDA (15)	randomised open label	ddI/3TC (189) versus ZVD/3TC (187)	efavirenz	67% vs 63%	67% vs 63%	158 vs 163	up to week 48: 14% vs 26%
FTC 301 (16)	randomised dubble blind	ddI/FTC (286) versus d4T/ddI (285)	efavirenz	78% vs 59%***	67% vs 50%***	168 vs 134	up to week 60: 7% vs 15%
Gilead 903 Study(17)	randomised dubble blind placebo controlled	TDF/FTC (299) versus d4T/3TC (303)	efavirenz	82% vs 81%	not available	169 vs 167	up to week 48: 9% vs 9% up to week 96: 14% vs 15%

Table 1. Major characteristics and parameters of effectiviness of the seven important clinical trials comparing different backbones of during 48 to 96 weeks of treatment
HLA-B57 screening test not done at inclusion
Degree of significance between treatment arms * p< 0,05 ** p<0,005 ***p<0.001

2.3 Resistance development during treatment with anti-retroviral backbones

Inadequate compliance is the most important cause of virologic failure and resistance development **(23,24)**. Repeated virologic failure with cumulation of resistances will lead to a decrease of the number of CD4 cells (immunologic failure), leading to HIV-related diseases, AIDS and death (clinical failure).
Development of resistance varies per class of anti-retroviral drugs and also within a class of antiretrovirals. For NRTIs, the development of resistance after initiation of cART is stongly associated with adherence. Resistance to antiretrovirals from the start of cART will develop

first and during follow-up in highest frequency to lamivudine, followed by development of resistance to NNRTIs, NRTIs and PIs **(32).**

A distinction between the different mutations to NRTI's is made between thymidine analoge mutations (TAMs), TAMs-associated mutations, evolving mainly during virologic failure when on therapy with thymidine analogues ZVD and d4T and the discriminatory mutations and the Q151M pathway mutations conferring for multiresistance. Mutations, an acumulation of mutations or the occurrence of multi-resistant mutations limit the number of effective combinations of NRTIs in the backbone for a second or third regimen.

For instance the K65R mutation (discriminatory mutation) can develop during failing therapy with TDF and will make ABC and ddI ineffective.

These drug-resistant viruses can be tranmitted and may limit the treatment options in treatment naïve patients.

The prevalence of transmitted drug resistance viruses since 2004 is similar in different Eropean countries and the Netherlands. In the Netherlands the prevalence of NRTI drug resistance in recent infection (naïve patients) is found to be around 5-6% and for intermediate or high level of resistance is around 2% **(33)**

Since2003 treatment guidelines recommend onbtaining a genotypic sequence at the start of cART.

3. Safety of anti-retroviral backbones

3.1 Grade 3 and 4, serious adverse events

The prevalence and incidence of grade 3 (severe adverse event) and grade 4 (potentially life threatening adverse event) adverse events (table according to NIAID, Division of AIDS) (19) provide information on the safety of anti-retrovirals. It is not always possible to determine which adverse events are caused by an individual drug or by the combination of drugs in a regimen. Grade 3-4 adverse events have major consequences for the patient and may lead to significant morbidity, hospitalisation and mortality. The medication must almost always be stopped, leading to an increased risk of resistant mutations, decrease in CD4 cell count and resulting impairment of physical condition and a lower quality of life **(22,23,24,31).**

Adverse events in the studies with mainly naive patients show highly variable incidences of grade 3 and 4 adverse events, ranging from 0-57%. On the basis of these studies, it is not possible to determine a certain pattern of side-effects. It is not clear which side-effects can be linked to the individual NRTI, to the backbone or other drugs. In some studies all grade 2-4 side-effects are summarised without full details **(10,14,16).** In other studies report only a selection of grade 3 and 4 clinical and or only laboratory adverse events are reported **(11,12).**

The percentage of patients stopping study drugs because of adverse events ranged up to 34% (see table1). Several adverse events with changing severity have been associated with NRTIs (**34).**

Anemia, neutropenia and thrombocytopenia

Anemia and neutropenia (granulocytopenia) occur are 1.1-9.7% of the patients treated with ZVD. Higher percentages is seen in patients with AIDS, 15-61% **(35).** Serious grade 3 of 4 anemia and neutropenia are relatively rare with earlier initiation of treatment. Hematologic toxicity is more often seen with ZVD and rarely to never in treatment with other NRTIs. Combinations of NRTIs with other hemato-toxic medication may increase the incidence of serious anemia and neutropenia **(35).** Serious grade 3 of 4 thrombocytopenia due to cART, necessitating thrombocytes transfusions have been reported **(35).**

Pancreatitis:
In the older studies pancreatitis was seen in 4-7% of patients treated with ddI and d4T. In 6% of these patients pancreatis was fatal **(35).** Combinations of ddI/d4T double the risk and ddI/TDF also increase the risk of development of pancreatitis **(36)**.
In the ACTG studies from October 1989 through July 1999 the overall pancreatitis rates were 0.61 per 100 person-years clinical and 2.23 per 100 person-years clinical/laboratory **(36).** The incidence of pancreatitis in the EuroSida cohort decreased over the years with earlier start of therapy and with higher CD4 cell counts. The incidence was 0.127 per 100 person-years over the years 2001-2006 **(38).**
Lactate acidosis (mitochondrial toxicity):
Lactate acidosis is a serious complication of the treatment with NRTIs, which occurs in around 0.9 times per 1000 years of treatment and often leads to serious morbidity and mortality **(35).**
In vitro studies have shown that inhibition of DNA polymerase gamma and other mitochondrial enzymes by NRTIs may lead to mitochondrial disfunction and cellular toxicity.
The clinical symptomatology of NRTI-induced mitochondrial toxicity consists of steatosis, hepatitis, lactate acidosis, myopathy, nephrotoxicity, peripheral neuropathy and pancreatitis. Studies with NRTIs in enzym assays and in cell cultures have shown that the following NRTIs are responsible for this mitochondrial toxicity, to a decreasing extent: ddI > d4T > ZVD **(39)**. DNA polymerase gamma inhibition is not found in normal concentrations of ABC, 3TC and TDF **(39).**
Lipodystrophy:
Three forms of lipodystrophy are distinguished: lipoatrophy caused by loss of subcutaneous fat, fat accumulation or lipohypertrophy and mixed forms. It was described with cART in 1997 and may occur in all combinations of cART medication with a prevalence between 2-84%. Lipo-accumumulation like buffelo-hump and "crix belli" may be caused by PIs, lipoatrophy by NRTIs. Lipoatrophy may occur shortly after initiation of cART. In a large observational cohort, 62% of the patients who developed lipoatrophy has symptoms within one year. In this cohort a highly significant correlation was found between lipoatrophy and the use of d4T **(40)**. It has been shown in observational cohort studies, clinical trials and in pathologic studies that lipoatrophy is specifically related to the use of NRTI especially d4T and in to a lesser extent to ZVD. Host factors have a modulating effect on the risk and the severity of lipoatrophy **(2).**
The development of lipoatrophy is a serious complication which often leads to a marked decrease of the quality of life. In clinical studies is was shown that lipoatrophy improved by the replacement of ZVD or d4T by ABC **(41)** or TDF **(42).**
Peripheral neuropathy
The occurrence of peripheral neuropathy is a well known complication of HIV-infection itself or due to a toxic effect on mitochondria induced by some NRTIs. Its incidence increases with the extent of immunodeficiency and older age. Patients who develop peripheral neuropathy tend to do so shortly after exposure to antiretroviral therapy and certain subgroup of patients are found to be more susceptible than others **(43).**
With ddI use the incidence of medication related sensoric neuropathy was 6.8 cases per 100 person years. In one study the relatieve risk is 1.4 fold higher in d4T use and 3.5 times higher in the combination of ddI/d4T compared to other NRTIs **(44).** In an other study peripheral neuropathy was reported in 3.0 cases per 100 person-years for ZVD

monotherapy and in 2.2 cases per 100 person-years for ZVD/ddl **(43).** Sensoric neuropathy has not been associated with the use of ABC,3TC, FTC and TDF.

Rash (hypersensitivity reaction) and muscle disorders

Drug hypersensitivity reactions are an important cause of morbidity in HIV-infected patients. The hypersensitivity reactions can be caused by each of the antiretroviral drugs in the cART regimen or by other concomitend prescribed drugs.

ABC is known for its hypersensitivity reaction usually appearing in the first six week after starting ABC therapy. Symptoms of this ABC related hypersensitivity reaction are nonspecific and can be difficult to distinguish from reactions to other drugs or conditions and can lead to serious complications and death if not recognized. The presence of HLA-B5701 antigen is highly predictive for the chance of developing this hypersensitivity reaction. ABC hypersensitivity reaction affects 5-8% of patients during the first six weeks of treatment **(18).**

Hypersensitivity reactions to 3TC, FTC, ddI, TDF have been reported but occur very rarely **(45).** Other forms of hypersensitivity reactions and rashes are related to the use of NNRTIs and PIs and are usually mild and self-limiting **(46).**

Other serious adverse events like rhabdomyolysis, myopathy and cardiomyopathy are very rare complications, which are not clearly related to NRTIs. **(46).**

Renal failure

Chronic kidney disease in HIV-positive persons can be caused by both HIV and traditional or non-HIV-related factors and antiretroviral drugs. Tenofovir has been associated with decline in renal funtion **(47,48,49).**

Tenofovir is mainly cleared by glomerular filtration and active tubular secretion through tubular transport proteins. Interactions and competition of different anti-retrovirals with these transport proteins can lead to renal toxicity and increased blood levels. The combination of TDF/ddI leads to ~ 30% increased ddI levels and ddI related toxicity.

Up to February 2006, 27 individual cases of renal failure with or without proteinuria or Fanconi syndrome (renal tubular acidosis) have been described with the use of TDF **(47).**

During a follow-up of 144 weeks of 600 patients in the 903 Study **(17,50)** comparing d4T/3TC/EFV with TDF/3TC/EFV no significant increases in mean creatinine level were seen in the 299 patients treated with tenofovir. In the Heat study **(10)** comparing ABC/3TC and TDF/FTC and in Study 934 **(13)** comparing ZVD/3TC and TDF/FTC during an obserervation period of respectively 96 weeks and 48 weeks no significant difference in renal function could be shown.

In the Swiss HIV Cohort Study **(48)** 363 treatment-naive patients or patients with treatment interruptions of more than 12 months starting either a TDF-based cART and 715 patients on a TDF-sparing regime were compared for the time to reach a 10 ml/min reduction in calculated GFR (cGFR). Apart from diabetes mellitus, higher baseline cGFR (by 10 ml/min), TDF use and boosted PI use were significantly associated with an increased risk for reaching a 10 ml/min reduction in cGFR during an observation time of two years.

During a median follow-up of 3.7 years in the EuroSida Study Group **(49)** 225 (3.3%) persons progressed to chronic kidney disease during 21.482 person-years follow-up, an incidence of 1.05 per 100 person-years follow-up. After adjustment for traditional factors associated with chronic kidney disease, increasing cumulative exposure to TDF and the PIs, indinavir, atazanavir and lopinavir/ritonavir were associated with a significantly increased rate of decline in renal function. No other antiretroviral drugs were associated with increased incidence of chronic kidney disease.

In a prospective observational cohort study at Johns Hopkins **(51)** patients taking both TDF and NRTIs experienced an initial decline in cGFR during the first 180 days of therapy, but cGFR stabilized between 180 and 720 days. In this study there was no difference between TDF and NRTI use in more than 25% or 50% decline in cGFR at 1 or 2 years or in change in cGFR at 6, 12, or 24 months. Those taking TDF and a PI/ritonavir had a greater median decline in cGFR than those taking TDF and a NNRTI at 6 months. There was no difference in median cGFR decline between those on an NRTI/PI/ritonavir versus those on an NRTI/NNRTI regimen.

The reversibility of TDF-related nephrotoxicity in 24 male patients who ceased TDF for renal impairment by retrospective assessment were determined **(52).** Median eGFR pre-TDF was 74 mL/min/1.73 m^2 (using the Modified Diet in Renal Disease equation) and fell to 51 mL/min/1.73 m^2 at TDF cessation and increased to 58 mL/min/1.73 m^2 in a median of 13 months after TDF cessation. This decline in cGFR, most recent versus pre-TDF is significant. Results were similar using the Cockcroft-Gault equation for cGFR. Only 10 patients reached their pre-TDF cGFR.

Many patients on antiretroviral therapy have multiple medical problems and may take other potentially nephrotoxic drugs. It has been clearly shown that taking TDF in combination with PI may increase a decline in renal function.

In a systematic review **(53)** of a total of 17 studies (including 9 randomized, controlled trials) a significantly greater loss of kidney function was seen among patients using TDF, compared with control subjects (mean difference in eGFR was 3.92 mL/min, as well as a greater risk of acute renal failure. There was no evidence that TDF use led to increased risk of severe proteinuria, hypophosphatemia, or fractures.

Thus in some well designed randomized prospective trials **(10,17,50)** no decline in renal function during treatment with TDF has been noted. Some observational stusies have found evidence of mild decrease in kidney function in TDF treated patients and when TDF related renal toxicity was present it was not always fully reversible**.**

Cardiovascular risk and lipids

The risk of cardio vascular disease (CVD) and other non-AIDS conditions increases with age, but prevalence of these diseases by age is greater in HIV-positive populations. In a case-control study of HIV-infected patients and healthy HIV-negative individuals from an observational database comparing rates of 6 comorbidities,CVD, hypertension, renal failure, osteoporosis, diabetes, and hypothyroidism to be higher in HIV-infected patients **(54).**

Numerous large observational cohort studies in Europe and the USA have found higher rates of acute myocardial infarction (MI) or coronary heart disease (CHD) in patients with HIV. (5-10) In a cross-sectional study of HIV-infected participants and controls without pre-existing CVD preclinical atherosclerosis assessed by carotid intima-medial thickness measurements in the internal/bulb and common carotid regions in HIV-infected participants and controls after adjusting for traditional CVD risk factors showed that HIV infection was accompanied by more extensive atherosclerosis **(61).**

The higher risk among patients with HIV-infected patients held true for every age group analyzed and in multivariate analysis adjusting for demographics and common cardiovascular risk factors confirm that HIV infection is an independent predictor of acute MI, conferring nearly a two-fold risk. The risk of myocardial infarcion is found to be associated with the cumulative use of PIs in these studies **(55,56,59,60).**

In the D.A.D cohort, a lage observational prospective cohort study with more than 30,000 HIV-infected patients in 212 clinics since 1999, it was found that ABC and ddI were

associated with a higher risk of acute MI within each CVD risk category defined by the Framingham Risk Score **(62).** Exposure to ABC within the most recent 6 months was associated with a 1.90 relative risk of acute MI. Subsequent analysis suggested cumulative use of ABC may also been associated with increased MI risk, although to a lesser extent than recent use **(63).** Since that first publication, several reports on MI risk associated with ABC have appeared, and some of these analyses have not implicated ABC as an MI risk factor. Several studies have focused on possible mechanisms that may explain the increased risk on MI in patients taking ABC. In the largest analysis, SMART study investigators found higher levels of hsCRP and IL-6 in patients taking ABC than in patients not taking ABC **(64)** However, a study of 13 biomarkers in virologically suppressed patients taking ABC/3TC vs TDF/FTC found no significant change in either group after 48 weeks **(65).** The results of the DAD study **(62)** could have been confounded by te so-called allocation biases such as high cardiovascular risk and renal function. In the Veterans Affairs Study a weak correlation between ABC use and MI was found, disappearing entirely after statistical adjustment for renal disease **(66).**

In November 2008, DHHS guidelines reclassified abacavir from a preferred first-line agent to an alternate agent, partly because of these data on cardiovascular risk.

In the DAD study correcting the increased relative risk for antiretroviral-associated CVD for lipds attenuated this CVD risk by around 10% **(55).** In the ACTG 5202 study **(11,12)** fasting lipids at week 48 had increased more in the ABC/3TC arm than in the TDF/FTC arm (respectively; total cholesterol 0,87 mmol/L versus 0,67 mmol/L and triglycerides 0.28 mmol/L versus 0.03 mmol/L) with no significant difference between groups in the change in the ratio of total cholesterol to HDL cholesterol. In a systemic review of 7 clinical trials with a total of 3,807 paticipants, studying initial treatment in naïve subjects receiving 2NRTIs/efavirenz regimens the mean change in total cholesterol from baseline to 48 weeks was significantly greater in patients taking a non-TDF containing regimen **(67).**

Bone mineral density loss associated with HIV infection and cART

Many studies have documented an increased prevalence of osteopenia in HIV-infected individuals with dual x-ray absorptiometry bone densitometry (DEXA) scans. This finding is important since bone mineral density (BMD) predicts fracture risk **(68).** A higher fracture rate has been demonstrated among HIV-infected subjects compared with controls in a large healthcare system**.(69).** Many factors may play a role in the increased prevalence of osteopenia like vitamine D deficiency, low body mass, aging, corticosteroid use, alcoholism and HIV-infection.

Decreased BMD has been found in both treatment-naive and treated HIV-infected patients. Ongoing BMD loss over time has been observed in some treatment studies, although it is uncertain whether it is due to drug toxicity since it is difficult to differentiate between effects associated with antiretrovirals and other factors. In addition the presence and strength of antiviral-related factors is difficult to ascertain as combinations of classes of antiretroviral drugs are used.

In the GS 903 study comparing d4T/3TC and TDF/3TC, each combined with efavirenz in treatment-naive patients, after an an initial decrease in BMD was found in both study arms but stabilized after 24 weeks. By week 144, the mean decrease in BMD of the spine was significantly different 0.9% in the d4T/3TC arm and 2.2% in the TDF/3TC arm. At baseline there was a relatively high incidence of both osteopenia and osteoporosis in both study arms, but there was no significant difference in rates of new-onset osteopenia or progression to osteoporosis through week 144 **(70).**

In the STEAL study, 360 virologically suppressed patients were randomized to switch their current NRTIs to either ABC/3TC or TDF/FTC. No significant change in spine or hip T scores were observed in the ABC/3TC arm, but BMD at spine and hip decreased in the TDF/FTC arm, and the difference between the regimens was statistically significant at weeks 48 and 96 **(71).**

In a study comparing the effect of TDF versus ABC based regimens on BMD, BMD decreased early during therapy in both arms before stabilizing. The mean loss of BMD was statistically greater with TDF and the loss correlated with biomarkers of bone turnover **(72).** Similar results were obtained in an other study comparing the safety aspects of ABC/3TC and TDF/FTC in 385 treatment-naive patients **(73).**

In the ACTG 5202 metabolic substudy, there was an initial reduction in BMD in all stady arms, which stabilized after 48 weeks. A significantly greater loss of BMD was seen at week 96 with TDF/FTC versus ABC/3TC. This included a significant 2% greater reduction in lumbar spine BMD and a significant 1.5% greater reduction in hip BMD. No difference was found in fracture rates between study arms at week 48 **(74).**

In the bone substudy of this trial, the initiation of antiretroviral therapy was associated with a decrease in bone mass of 2% to 4% that was independent of the regimen selected and stabilized by week 48; this decrease was greatest in patients who started a regimen that contained TDF **(75).**

Thus overall, BMD appears to decline to some degree during the first several months after initiation of cART, regardless of regimen, but the decline may be slightly greater with TDF containing regimens. However, there are no conclusive data showing that therapy-associated reductions in bone mineral density are also associated with an increased rate of fractures.

3.2 Documentation

The clinical documentation of the combinations is summarised in Table 2

	Number of clinical trials*	Years since registration
Zidovudine/Lamivudine or emtricitabine	532/23	>10 Emt: 8
Didanosine/Lamivudine or emtricitabine	165/10	>10 Emt: 8
Abacavir/Lamivudine or emtricitabine	160/15	> 10 Emt: 8
Tenofovir/emtricitabine or Lamivudine	78/115	>10 >10

Table 2. Documentation

* according to the definition of National Institute of Health/PubMed (www.ncbi.nih.gov)

4. Tolerability of anti-retroviral backbones

4.1 Grade 1 and 2, mild to moderate side-effects

The tolerability of a cART regimens is an important predictor of durability and long-term succes. Grade 1(mild adverse event) and grade 2 (moderate adverse event) **(19)** may have a

significant influence on compliance and quality of life **(22,26)** and on the durability of a certain combination. It is not always evident which drug in a cART regimen is responsible for which side-effect. The HIV-infection as such or complications of opportunistic infections may lead to symptoms marked as adverse events of anti-retroviral medication.
General symptoms as fatigue, pain, anorexia, sleep and concentration disturbances occur frequently **(46).**
It is difficult to give a reliable estimation of the relative incidence of different grade of adverse events, based on the EMEA and FDA data **(76)**, because of the relative lack of randomised comparative studies with extended follow-up and asufficient number of participants.
Cohort studies yield better insight as to why patients switch or stop certain antiretroviral drugs and how long they keep using the same regimen, in comparison with randomised studies which usually have a limited follow-up time.
In the older cohort studies high rates of toxicity driven changes in antiretroviral drugs were common. For instance in the Swiss HIV Cohort Study, with 2,674 patients, 35% stopped treatment with at least one drug during the observation period of 3.2 years because of adverse events and/or intolerability and 41% stopped the combination of anti-retroviral drugs at least once or completely changed to another combination **(77).**
In the Italian ICONA-cohort **(78),** 36% of the 862 patients stopped because of side-effects during study period of 45 weeks and only 5% because of virologic failure.
Earlier initiation of cART, lower pill burden and dosing schemes of once or twice daily, together with declining toxicity, have improved tolerability.
In the Athena-cohort the incidence per 100 patient years of toxicity driven changes of cART during the first 3 years after the start of therapy decreased from 29% in 1996 to 15% in 2008. Significant decline in toxicity driven changes of cART started to be apparent after calendar year 2000. The incidence of toxicity driven changes of cART is highest in the first 3 month after initiation.

5. Easy of use

5.1 Ease of use (dosage frequency, number of tablets per day)

The combinations of ABC/3TC, TDF/FTC and ddI/FTC or 3TC can be given once daily. ZVD/3TC (Combivir®)has to be given twice daily. The other combinations are given once or twice daily. The combinations of ABCbacavir/Lamivudine (Kivexa®, Epzicom®) and TDT/FTC (Truvada ®) can be given as one tablet per day. TDT/FTC in combination with efavirenz can be given in one tablet (Atripla ®)
DdI is given 2 hours before or after food. The rest of the drugs can be taken irrespective of food.

6. Applicability

6.1 Availability of different formulations

Liquid or dispersible formulations are available for ddI.

6.2 Drug interactions

Abacavir
Abacavir is not significantly metabolised by CYP450, which makes serious reactions regarding inhibition or induction of CYP450 enzymes unlikely **(80).** No interactions were seen with adefovir, amprenavir, indinavir, ZVD and 3TC **(50).**

Enzymeinducers like rifampicin, phenobarbital and phenytoin may decrease the plasma concentrations of abacavir to a minor extent through an effect on UDP-glucuronyltransferases [72].
Alcohol may decrease the AUC of abacavir by 40% **(81,82).**
Didanosine
The AUC of ddI doubles during simultaneous use of ganciclovir. Didanosine has no significant effect on the pharmacokinetics of zidovudine **(83).**
No clinically relevant interaction occurs between ddI with ritonavir, nevirapine, emtricitabine and nelfinavir **(84).**
Ribavirine may increase intracellular levels of ddI. The relevance of this is unknown.
Didanosine decreases the bioavailability of ciprofloxacin during simultaneous intake. It is recommended to take ciprofloxacin an hour before or at least 4 hours after ddI **(84).**
Didanosine showed no interaction with indinavir and fluconazole. Ketoconazole and itraconazole increase the AUC of ddI, maar these interactions do not appear te be very relevant.
The AUC of ddI increases by 50% in combination with tenofovir often leading to ddI toxicity **(3).**
Xanthine oxidase plays a role in the metabolism of didanosine, interactions with inhibitors of xanthine oxidase, like allopurinol, may theoretically decrease the clearance of didanosine.
Emtricitabine
Tenofovir and FTC do not affect each other's pharmacokinetics **(85, 86).** Emtricitabine is metabolised to a limited extent and is excreted unchanged in the urine through glomerular filtration and active tubular secretion**(85).** Interactions regarding to inhibition of active tubular secretion cannot be excluded, maar have not been studied **(85).**
Emcitabrine shows no pharmacokinetic interactions with protease inhibitors or with ddI **(85).**
Lamivudine
Lamivudine shows few metabolic interactions. The drug is excreted in an unchanged form through glomerular filtration and active tubular secretion **(87, 88).**
No interaction is seen with ZVD and ddI **(87, 88)**.
Trimethoprim may decrease active tubular secretion, increasing the AUC of lamivudine by 40% **(87, 88)**. Applications of high dose co-trimoxazole in pneumocystis carinii infections should not be combined with lamivudine **(87)**. There is inadequate documentation on a possible interaction with intravenous ganciclovir or foscarnet. This combination should be avoided.
Tenofovir
Tenofovir is mainly excreted uchanged in the urine through glomerular filtration and active tubular secretion **(90,91)**. Interactions regarding to inhibition of active tubular secretion cannot be excluded, but have not been studied **(90).**
Tenofovir and FTC have no effect on each other's pharmacokinetics **(85, 86,91).**
The AUC of TDF increases by 30% in combination with lopinavir and ritonavir or atazanavir **(92,93).** Tenofovir may decrease the AUC of atazanavir by 25%. The AUC of lopinavir increases by 15% by tenofovir. Tenofovir shows no interaction with saquinavir (**91**).
The AUC of ddI increases by 50% in combination with tenofovir **(91)**. This may increase the risk of pancreatitis and other ddI related toxicity. The AUC of atazanavir decreases by 25% in combination with TDF **(86).**
Tenofovir showed no interactions with indinavir, methadon, ribavirine or rifampicin **(91,93, 94).**

Zidovudine
Zidovudine is mainly glucuronidated. The drug may theoretically show interactions with a large number of drugs which are also excreted through glucuronidation, like aspirin, NSAIDs, penicillins and oxazepam. Very limited data on the relevance of these possible interactions is available (**95).**
The bioavailability of zidovudine may be decreased to a limited extent (22%) by simultaneouse intake with food (**96).**
The renal clearance of zidovudine decreases by 50% during simultaneous use of co-trimoxazole (**96).** This interaction is only relevant in disturbed glucuronidation of zidovudine.
Rifampicin lowers the AUC of zidovudine by 50%, an interaction with rifabutin is not very relevant, a 14% decrease of the AUC of zidovudine was seen (**96)**.
The AUC of ZVD increases by 75% in combination with fluconazole (**96).**
Zidovudine may cause an unpredictable interaction with phenytoin (increase of decrease of the phenytoin levels). Phenytoin levels have to be checked on a regular basis.
Atovaquone increases the AUC of zidovudine by 35%. Valproic acid and methadone may also lead to an increase in the AUC of zidovudine, but little data are available.
Zidovudine is antagonistic in combination with ribavirine or stavudine.
Nephrotoxic or myelosuppressive drugs may increase potential side-effects of ZVD (SPC on zidovudine).

6.3 Approved indications

There are no major differences in the approved indications. The applicability in children is described in 5.5.
Treatment co-infections
Lamivudine, emtricitabine and tenofovir also have anti hepatitis B virus activity. An advantage of these drugs is that "two in one" treatment is possible It is recommended that lamivudine or emtricitabine should be combined with tenofovir (97) in case of hepatitis B co-infection. Only lamivudine is approved for this indication.

6.4 Contra-indications

All drugs are contra-indicated in case of hypersensitivity.
Hypersensitivity to abacavir may be very serious.

6.5 Use in children and elderly

No dose adjustments are necessary in the elderly.
Zidovudine/lamivudine (Combivir) and abacavir/lamivudine (Kivexa) can be used in children from 12 years. The individual components can be used from 3 months.
Lamivudine can be used from 3 months
Didanosine tablets can be used from 6 years.
Tenofovir and emcitabine are only applicable in adults.

6.6 Use in renal and hepatic disease

A dose reduction is necessary in case of renal function impaiment. Abacavir/Lamivudine should not be used when the creatinine clearance is lower than 50 ml/min. Tenofovir/Emtricitabine should bot be used when the creatinine clearance is lower than 30 ml/min.

No dose adjustments are usually necessary in patients with liver disease.

6.7 Use in pregancy and lactation

A variable extent of mitochondrial damage may occur during in utero exposition to nucleoside-analogues. This may lead to hematologic toxicity or metabolic disturbances.
All drugs should be avoided during lactation. None of the combinations is recommended in case of pregnancy, but they are usually not absolutely contra-indicated.

6.8 Special precautions

Zidovudine/Lamivudine (Combivir)	Monitoring of hematologic parameters (ZVD) Lowering of the dosage of ZVD in abnormal hematologic parameters Therapy cessation during signs of pancreatitis (ZVD and 3TC) Lactic acidosis has been described. Therapy should be stopped in case of hyperlactatemia or metabolic acidosis Use with great caution in case of hepatomegaly, hepatitis or risk factors for liverdiseases (3TC) Cessation of L may lead to increased symptoms in patients who also have hepatitis B.
Didanosine/Lamivudine	Great caution with pancreatitis in the anamnesis (ddI and 3TC) Peripheral neuropathy may occur (ddI) Changes in the retina and N.opticus are to be checked in children (ddI) Use with great caution in case of hepatomegaly, hepatitis or riskfactors for liverdiseases (3TC) Lactic acidosis has been described. Therapy should be stopped in case of hyperlactatemia or metabolic acidosis (ddI and 3TC) Patients with hepatitis B or C have an increased risk on serious hepatic side-effects (ddI) Lipodystrophy may occur (ddI) Cessation of L may lead to increased symptoms in patients who also have hepatitis B.
Abacavir/Lamivudine (Kivexa)	Cessation of therapy during signs of pancreatitis (ABC and 3TC) Lactic acidosis has been described. Therapy should be stopped in case of hyperlactatemia or metabolic acidosis Use with great caution in case of hepatomegaly, hepatitis or risk factors for liverdiseases (3TC) Lipodystrophy may occur (3TC) Patients with hepatitis B or C have an increased risk on serious hepatic side-effects Cessation of 3TC may lead to increased symptoms in patients who also have hepatitis B.
Tenofovir/Lamivudine	Tenofovir may lower the BMD (TDF) No not use in case of the HIV-1 K65R mutation (TDF) Lactic acidosis has been described. Therapy should be stopped in case of hyperlactatemia or metabolic acidosis (TDF) Cessation of L may lead to increased symptoms in patients who

	also have hepatitis B. Use with great caution in case of hepatomegaly, hepatitis or risk factors for liverdiseases (3TC) Renal function should be checked. Combination with nephrotoxic drugs is not recommended (3TC)
Tenofovir/Emtricitabine (Truvada)	Do not combine with lamivudine Combination with a third nucleoside analogue is not recommended beause of possible virologic failure. The tablet contains lactose. Renal function should be checked. Combination with nephrotoxisc drugs is not recommended (TDF) No not use in case of the HIV-1 K65R mutation (TDF) Tenofovir may lower the bone mineral density (TDF) Patients with hepatitis B or C have an increased risk on serious hepatic side-effects (TDF) Cessation of TDF/FTC may lead to increased symptoms in patients who also have hepatitis B.
Didanosine/Emtricitabine	Great caution with pancreatitis in the anamnesis (ddI) Peripheral neuropathy may occur (ddI) Changes in the retina and N.opticus are to be checked in children (ddI) Lactic acidosis has been described. Therapy should be stopped in case of hyperlactatemia or metabolic acidosis (ddI) Lipodystrophy may occur (ddI) Patients with hepatitis B of C have an increased risk on serious hepatic side-effects (ddI) Lipodystrophy may occur (ddI)

7. Acquisition cost

Acquisition cost excluded for VAT in Euro ("vergoedingsprijs", Z-Index July 2011)

		Cost per month in Euro
Zidovudine/Lamivudine (Combivir)	2 dd 300/150 mg	379
Didanosine ER (Videx) Lamivudine (Epivir)	1 dd 400 or 250 mg (weight based) 300 mg in 1-2 doses	306/336
Abacavir/Lamivudine (Kivexa, Epzicom)	1 dd 600/300 mg	422
Tenofovir (Viread) Lamivudine (Epivir)	1 dd 245 mg 300 mg in 1-2 doses	510
Tenofovir/Emtricitabine (Truvada)	1 dd 200/245 mg	510
Didanosine ER (Videx) Emtricitabine (Emtriva)	1 dd 400 or 250 mg (weight based) 200 mg 1 dose	313/343

8. Conclusion

Optimal care requires individualized management and ongoing attention to relevant scientific and clinical information. The availability of new antiretroviral drugs since the introduction of the fist cART has expanded treatment choices. Guidelines are presented as recommendations if the supporting evidence warrants routine use in a particular situation and as considerations if data are preliminary or incomplete but suggestive. But the importance of adherence, emerging long-term complications of therapy, recognition and management of antiretroviral failure is often underestimated and there is but to often little data to guide our choices.

The judgement of the relative efficacy and safety of the various NRTI backbones in the treament of HIV infection is hindered by the fact that there are only few direct comparative studies. This makes it difficult to make firm statements concerning the pros and cons of the individual drugs concerning efficacy and safety.

In this InforMatrix manuscript, no firm conclusions are drawn by the authors. The purpose of this manuscript is to facilitate discussion on the properties of each treatment option for HIV by using only clinically relevant selection criteria by providing an up-to-date overview. The InforMatrix program will be made available in an interactive format on www.informatrix.nl. By means of the program, the user can assign a relative weight to each main selection criterion (with a total of 30 points to be distributed) and can judge the properties of each therapeutic option per criterion on the basis of his own personal expertise and/or the present document. Zero to ten points can be assigned to each treatment option on each criterion. The program is freely accessible.

The present InforMatrix manuscript is specific for the Netherlands, because the Dutch available formulations and Dutch prices were used. The most important part of the paper (efficacy, safety and tolerability) is internationally valid. Local adjustments are necessary for an optimal use of the method in other countries. This could also include price-adjustments for the individual hospitals in other countries.

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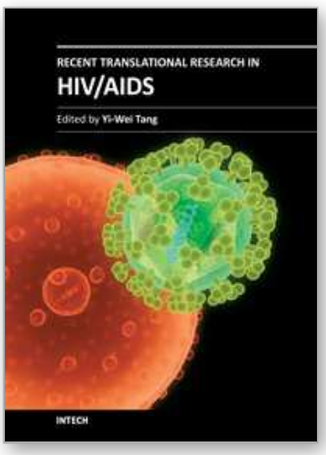

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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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