US006188988B1

(12) **United States Patent**
Barry et al.

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(45) **Date of Patent: *Feb. 13, 2001**

(54) **SYSTEMS, METHODS AND COMPUTER PROGRAM PRODUCTS FOR GUIDING THE SELECTION OF THERAPEUTIC TREATMENT REGIMENS**

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(73) Assignee: **Triangle Pharmaceuticals, Inc.**, Durham, NC (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/523,532**

(22) Filed: **Mar. 10, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/283,702, filed on Apr. 1, 1999.
(60) Provisional application No. 60/080,629, filed on Apr. 3, 1998.

(51) **Int. Cl.**[7] **G06F 17/60**
(52) **U.S. Cl.** **705/3**; 705/2; 706/45; 706/46; 706/47; 706/924
(58) **Field of Search** 705/2, 3, 1; 706/45, 706/46, 47, 10, 61, 924

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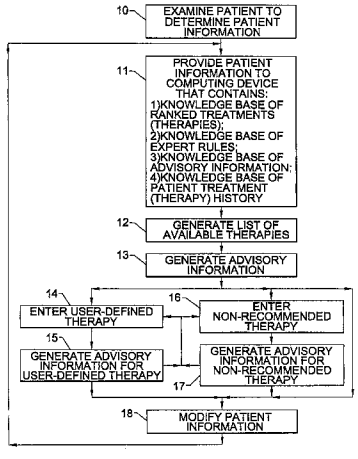
Assistant Examiner—John W. Hayes
(74) *Attorney, Agent, or Firm*—Myers Bigel Sibley & Sajovec

(57) **ABSTRACT**

Systems, methods and computer program products for guiding selection of a therapeutic treatment regimen for a known disease such as HIV infection are disclosed. The method comprises (a) providing patient information to a computing device (the computer device comprising: a first knowledge base comprising a plurality of different therapeutic treatment regimens for the disease; a second knowledge base comprising a plurality of expert rules for selecting a therapeutic treatment regimen for the disease; and a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of the different therapeutic treatment regimens; and (b) generating in the computing device a listing (preferably a ranked listing) of therapeutic treatment regimens for the patient; and (c) generating in the computing device advisory information for one or more treatment regimens in the listing based on the patient information and the expert rules.

66 Claims, 22 Drawing Sheets



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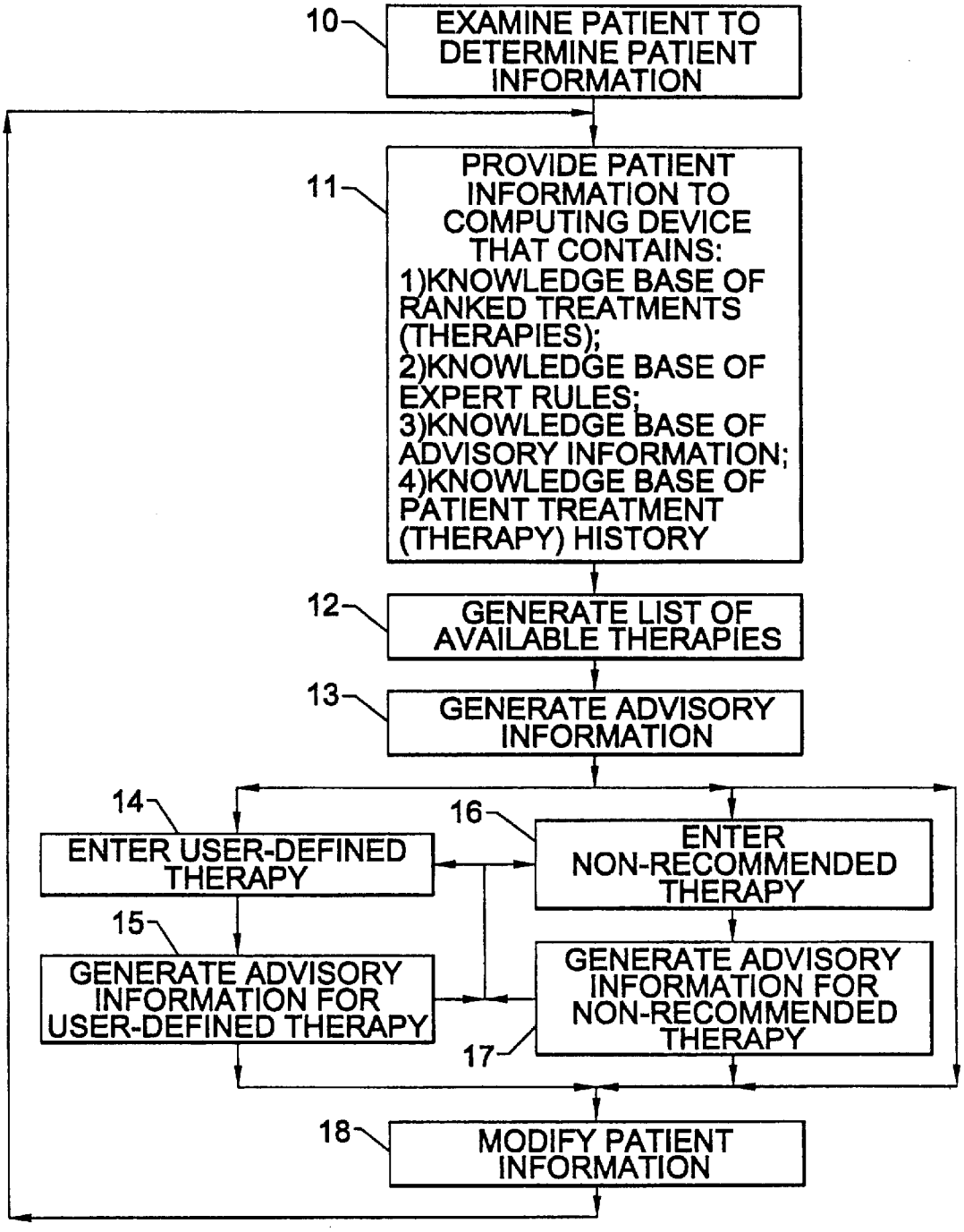

10
EXAMINE PATIENT TO DETERMINE PATIENT INFORMATION
11
PROVIDE PATIENT INFORMATION TO COMPUTING DEVICE THAT CONTAINS:
1)KNOWLEDGE BASE OF RANKED TREATMENTS (THERAPIES);
2)KNOWLEDGE BASE OF EXPERT RULES;
3)KNOWLEDGE BASE OF ADVISORY INFORMATION;
4)KNOWLEDGE BASE OF PATIENT TREATMENT (THERAPY) HISTORY
12
GENERATE LIST OF AVAILABLE THERAPIES
13
GENERATE ADVISORY INFORMATION
14
ENTER USER-DEFINED THERAPY
16
ENTER NON-RECOMMENDED THERAPY
15
GENERATE ADVISORY INFORMATION FOR USER-DEFINED THERAPY
GENERATE ADVISORY INFORMATION FOR NON-RECOMMENDED THERAPY
17
18
MODIFY PATIENT INFORMATION

FIG. 1.

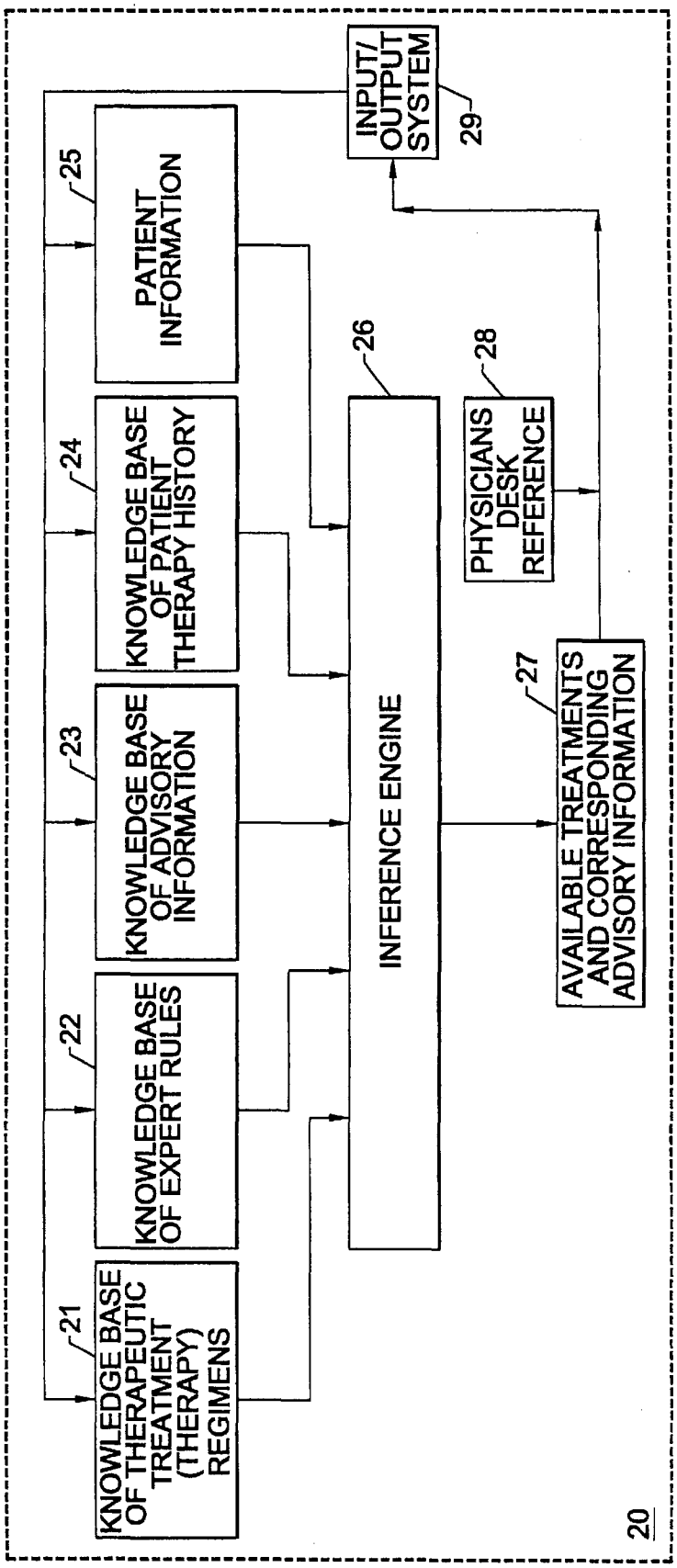

KNOWLEDGE BASE OF THERAPEUTIC TREATMENT (THERAPY) REGIMENS
21
KNOWLEDGE BASE OF EXPERT RULES
22
KNOWLEDGE BASE OF ADVISORY INFORMATION
23
KNOWLEDGE BASE OF PATIENT THERAPY HISTORY
24
PATIENT INFORMATION
25
INFERENCE ENGINE
26
PHYSICIANS DESK REFERENCE
28
AVAILABLE TREATMENTS AND CORRESPONDING ADVISORY INFORMATION
27
INPUT/ OUTPUT SYSTEM
29
20

FIG. 2.

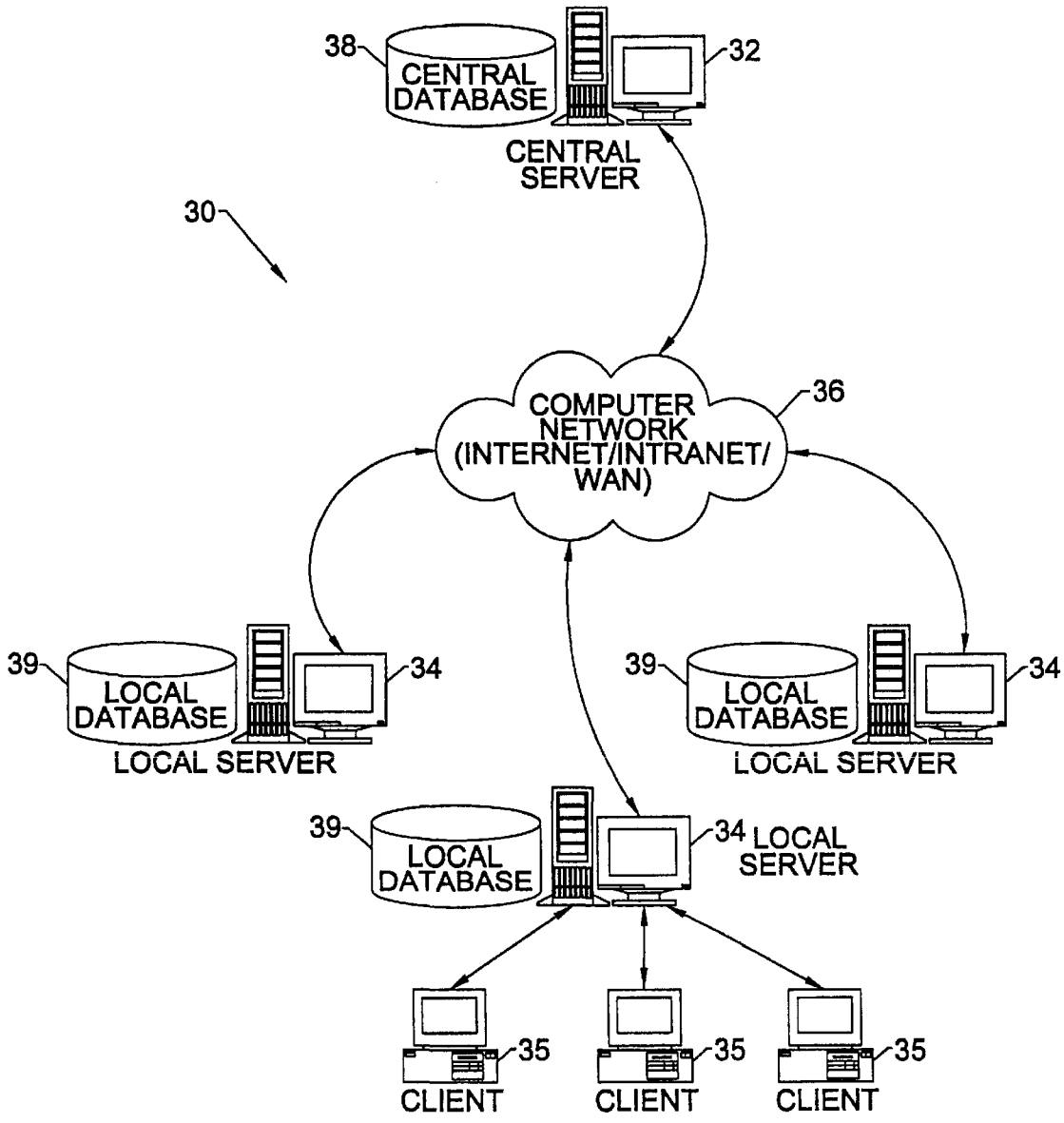

38
CENTRAL DATABASE
32
CENTRAL SERVER
30
COMPUTER NETWORK (INTERNET/INTRANET/ WAN)
36
39
LOCAL DATABASE
34
LOCAL SERVER
39
LOCAL DATABASE
34
LOCAL SERVER
39
LOCAL DATABASE
34 LOCAL SERVER
35
CLIENT
35
CLIENT
35
CLIENT

FIG. 3.

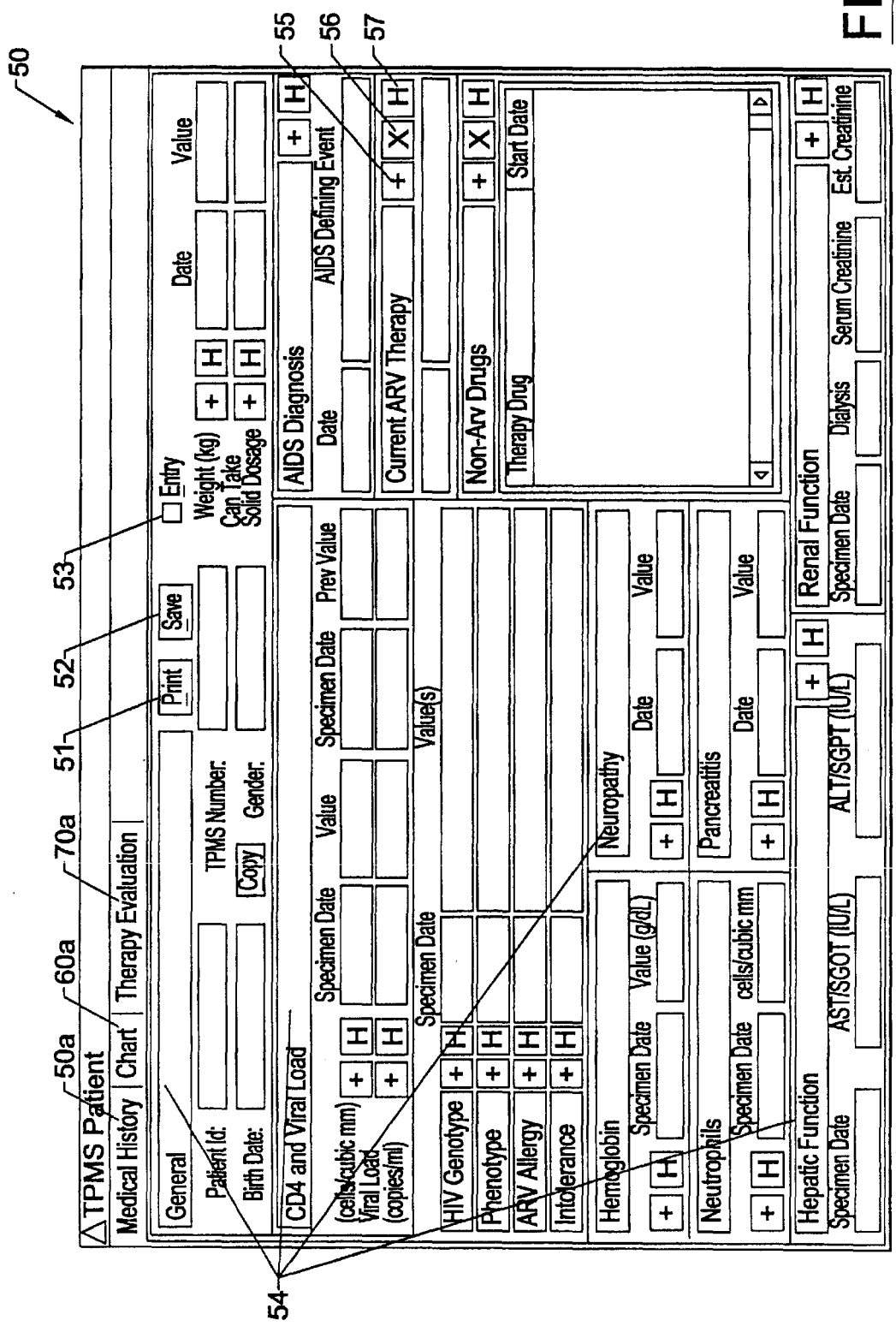

50
TPMS Patient
Medical History
Chart
Therapy Evaluation
General
Patient Id:
Birth Date:
TPMS Number:
Copy
Gender:
Print
Save
Entry
Weight (kg)
Can Take Solid Dosage
Date
Value
CD4 and Viral Load
Specimen Date
Value
Prev Value
(cells/cubic mm)
Viral Load (copies/ml)
HIV Genotype
Phenotype
ARV Allergy
Intolerance
Value(s)
Hemoglobin
Value (g/dL)
Neutrophils
cells/cubic mm
Hepatic Function
AST/SGOT (IU/L)
ALT/SGPT (IU/L)
Neuropathy
Pancreatitis
AIDS Diagnosis
AIDS Defining Event
Current ARV Therapy
Non-Arv Drugs
Therapy Drug
Start Date
Renal Function
Dialysis
Serum Creatinine
Est. Creatinine
50a
60a
70a
51
52
53
54
55
56
57

FIG. 4.

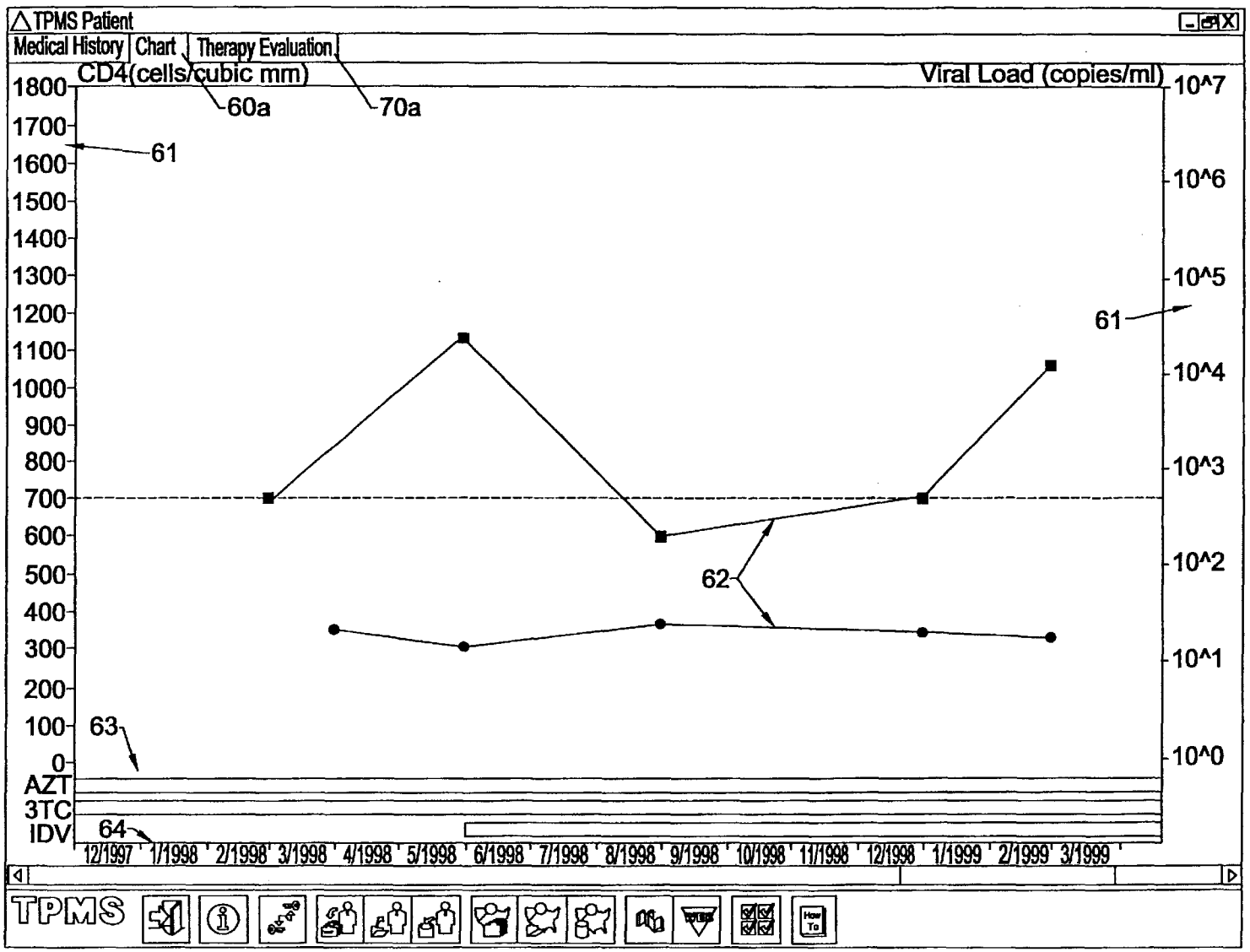
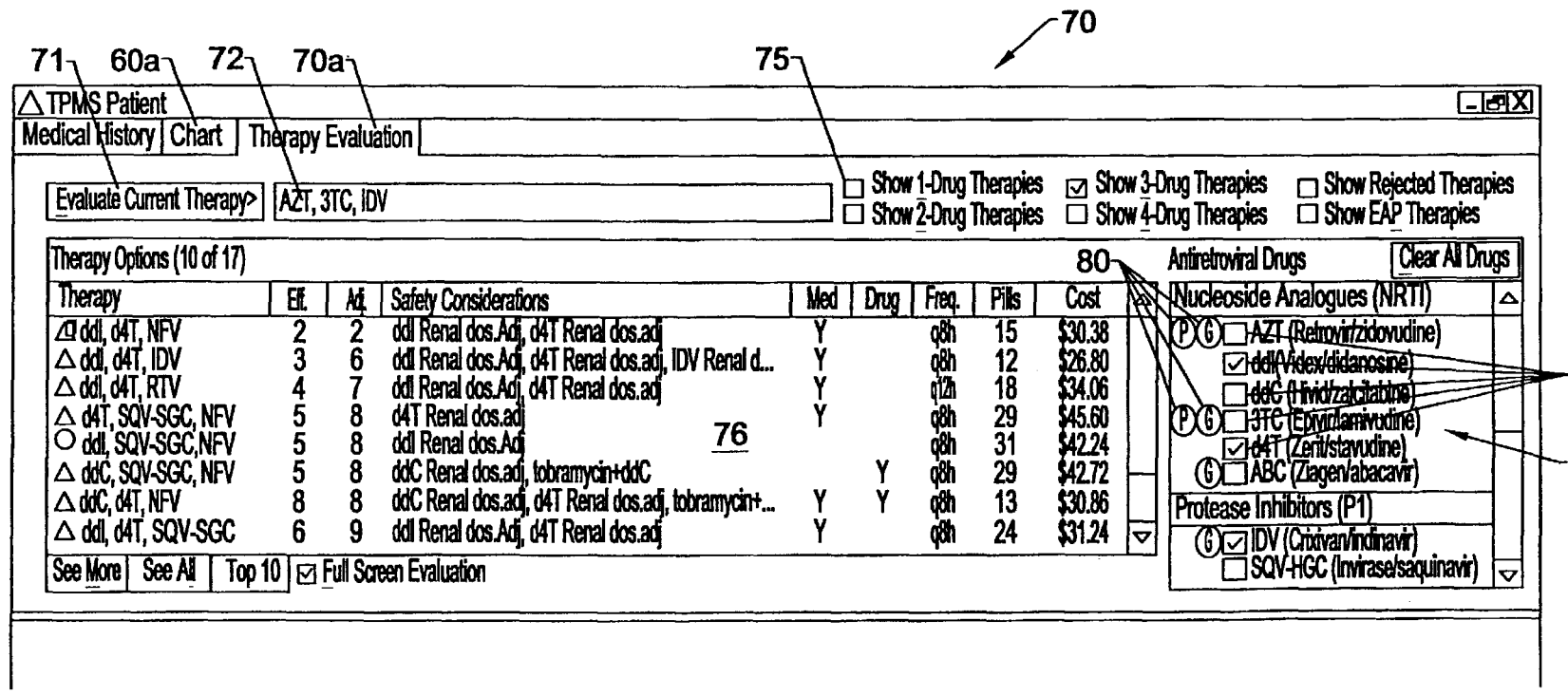

TPMS Patient
Medical History
Chart
Therapy Evaluation
CD4(cells/cubic mm)
Viral Load (copies/ml)
60
60a
70a
61
62
63
64
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
10^7
10^6
10^5
10^4
10^3
10^2
10^1
10^0
AZT
3TC
IDV
12/1997
1/1998
2/1998
3/1998
4/1998
5/1998
6/1998
7/1998
8/1998
9/1998
10/1998
11/1998
12/1998
1/1999
2/1999
3/1999
TPMS

FIG. 5.



TO FIG. 6B.

FIG. 6A.

FROM FIG. 6A.

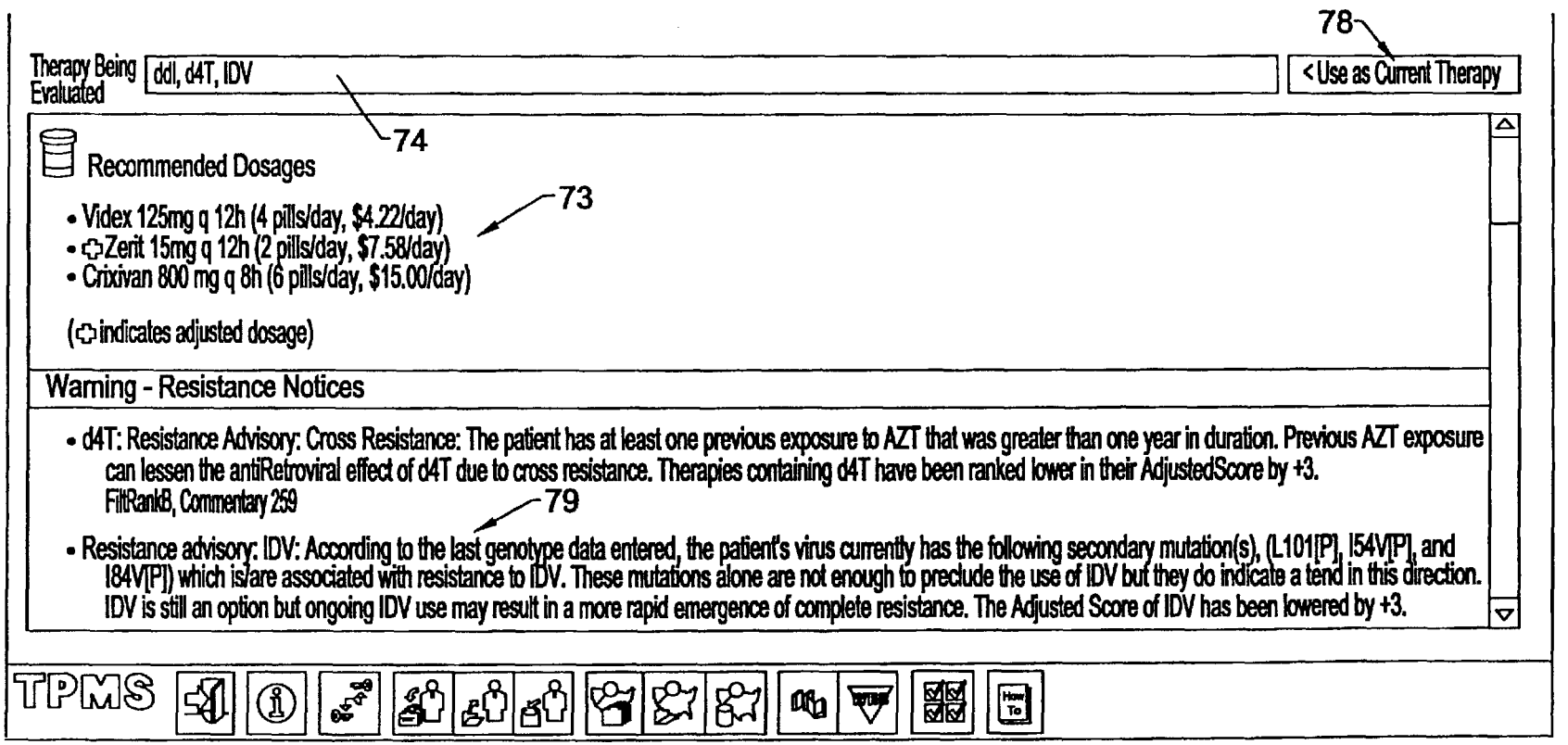


FIG. 6B.

Icon	Meaning
○	Indicates that there were no critical alerts for the therapy, however, general warnings and advisories should be read in the Therapy Details box.
◎	Indicates that there were no critical alerts for the therapy, however, general warnings and advisories should be read in the Therapy Details box. The book indicates that therapy has been studied and a reference is available to review.
△	Indicates a yellow alert. There is important information about this therapy that must be reviewed.
◬	Indicates a yellow alert. There is important information about this therapy that must be reviewed. The book indicates that therapy has been studied and a reference is available to review.
!	Indicates a red alert, which means critical and possible life-threatening situation may exist or may be created with this therapy. Information in the Therapy Details section must be read for this therapy to be considered.
!◎	Indicates a red alert, which means critical and possible life-threatening situation may exist or may be created with this therapy. Information in the Therapy Details section must be read for this thereapy to be considered. The book indicates that therapy has been studied and a reference is available to review.
X	Indicates the therapy is not recommended.

FIG. 7.

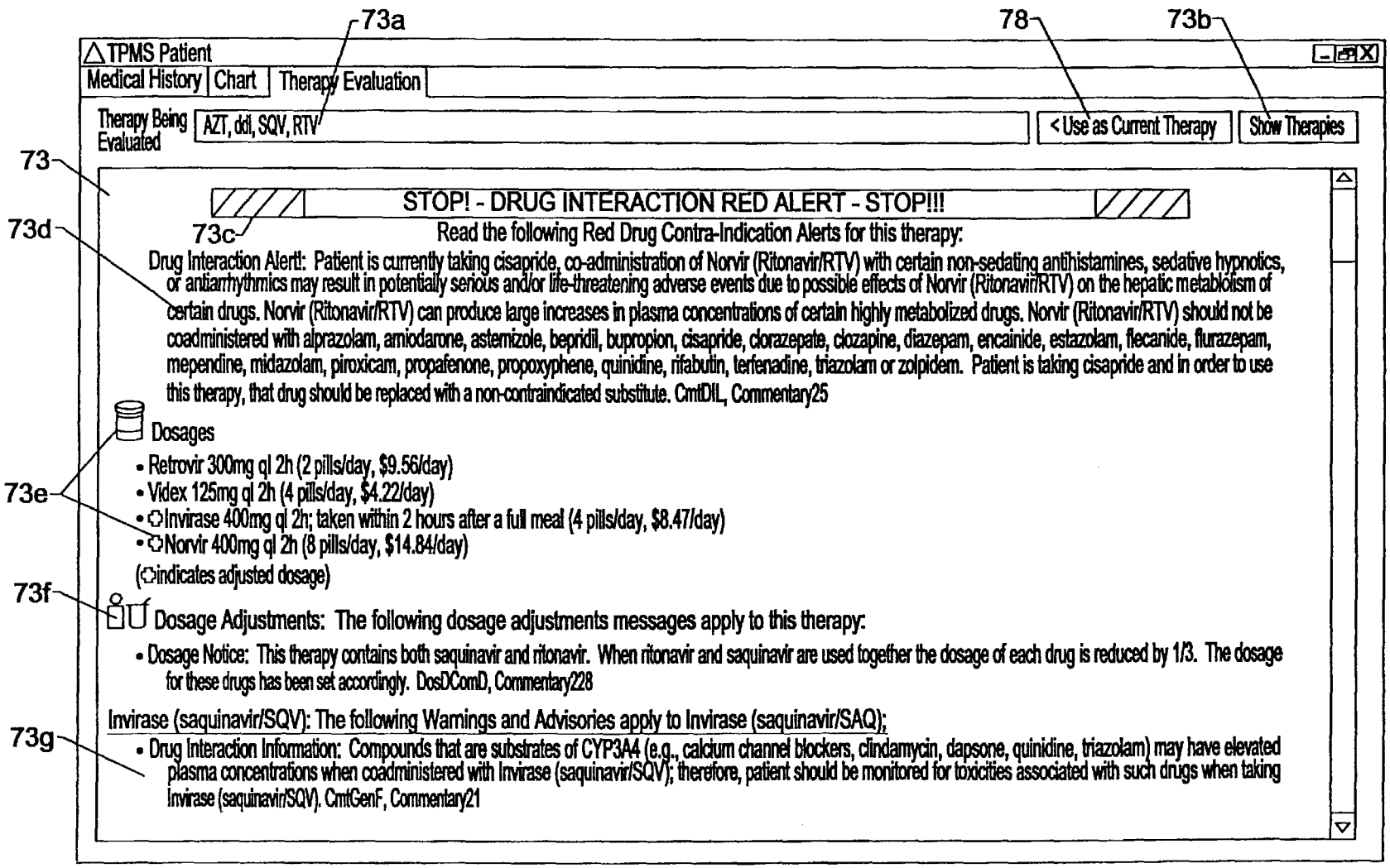

73a
78
73b
TPMS Patient
Medical History
Chart
Therapy Evaluation
Therapy Being Evaluated
AZT, ddI, SQV, RTV
< Use as Current Therapy
Show Therapies
73
73d
73c
STOP! - DRUG INTERACTION RED ALERT - STOP!!!
Read the following Red Drug Contra-Indication Alerts for this therapy:
Drug Interaction Alert!: Patient is currently taking cisapride, co-administration of Norvir (Ritonavir/RTV) with certain non-sedating antihistamines, sedative hypnotics, or antiarrhythmics may result in potentially serious and/or life-threatening adverse events due to possible effects of Norvir (Ritonavir/RTV) on the hepatic metabolism of certain drugs. Norvir (Ritonavir/RTV) can produce large increases in plasma concentrations of certain highly metabolized drugs. Norvir (Ritonavir/RTV) should not be coadministered with alprazolam, amiodarone, astemizole, bepridil, bupropion, cisapride, clorazepate, clozapine, diazepam, encainide, estazolam, flecanide, flurazepam, mependine, midazolam, piroxicam, propafenone, propoxyphene, quinidine, rifabutin, terfenadine, triazolam or zolpidem. Patient is taking cisapride and in order to use this therapy, that drug should be replaced with a non-contraindicated substitute. CmtDIL, Commentary25
73e
Dosages
• Retrovir 300mg ql 2h (2 pills/day, $9.56/day)
• Videx 125mg ql 2h (4 pills/day, $4.22/day)
• ⬡Invirase 400mg ql 2h; taken within 2 hours after a full meal (4 pills/day, $8.47/day)
• ⬡Norvir 400mg ql 2h (8 pills/day, $14.84/day)
(⬡indicates adjusted dosage)
73f
Dosage Adjustments: The following dosage adjustments messages apply to this therapy:
• Dosage Notice: This therapy contains both saquinavir and ritonavir. When ritonavir and saquinavir are used together the dosage of each drug is reduced by 1/3. The dosage for these drugs has been set accordingly. DosDComD, Commentary228
Invirase (saquinavir/SQV): The following Warnings and Advisories apply to Invirase (saquinavir/SAQ);
73g
• Drug Interaction Information: Compounds that are substrates of CYP3A4 (e.g., calcium channel blockers, clindamycin, dapsone, quinidine, triazolam) may have elevated plasma concentrations when coadministered with Invirase (saquinavir/SQV); therefore, patient should be monitored for toxicities associated with such drugs when taking Invirase (saquinavir/SQV). CmtGenF, Commentary21

FIG. 8.

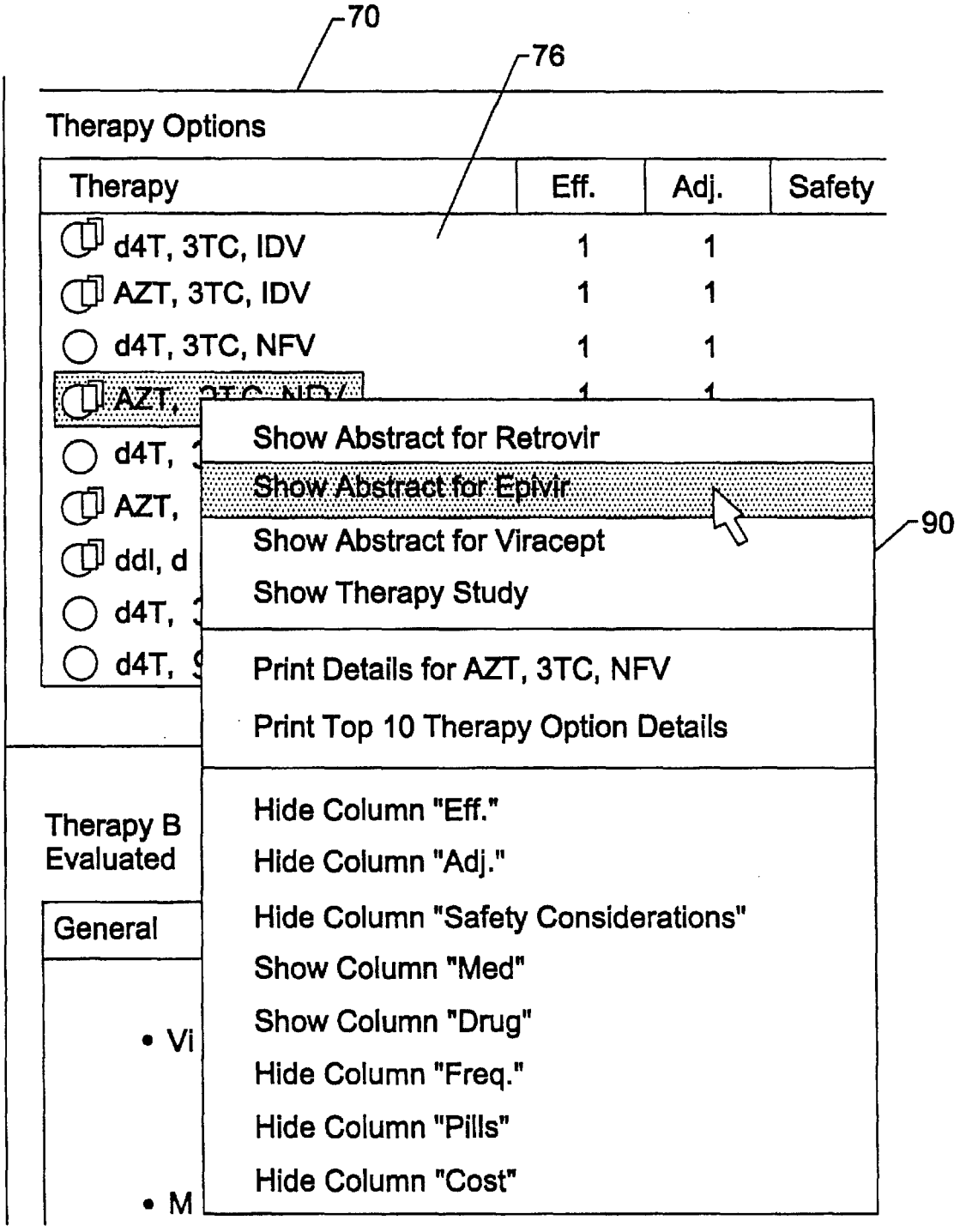

70
76
Therapy Options
Therapy
Eff.
Adj.
Safety
d4T, 3TC, IDV 1 1
AZT, 3TC, IDV 1 1
d4T, 3TC, NFV 1 1
Show Abstract for Retrovir
Show Abstract for Epivir
Show Abstract for Viracept
Show Therapy Study
90
Print Details for AZT, 3TC, NFV
Print Top 10 Therapy Option Details
Therapy B Evaluated
General
Hide Column "Eff."
Hide Column "Adj."
Hide Column "Safety Considerations"
Show Column "Med"
Show Column "Drug"
Hide Column "Freq."
Hide Column "Pills"
Hide Column "Cost"

FIG. 9.

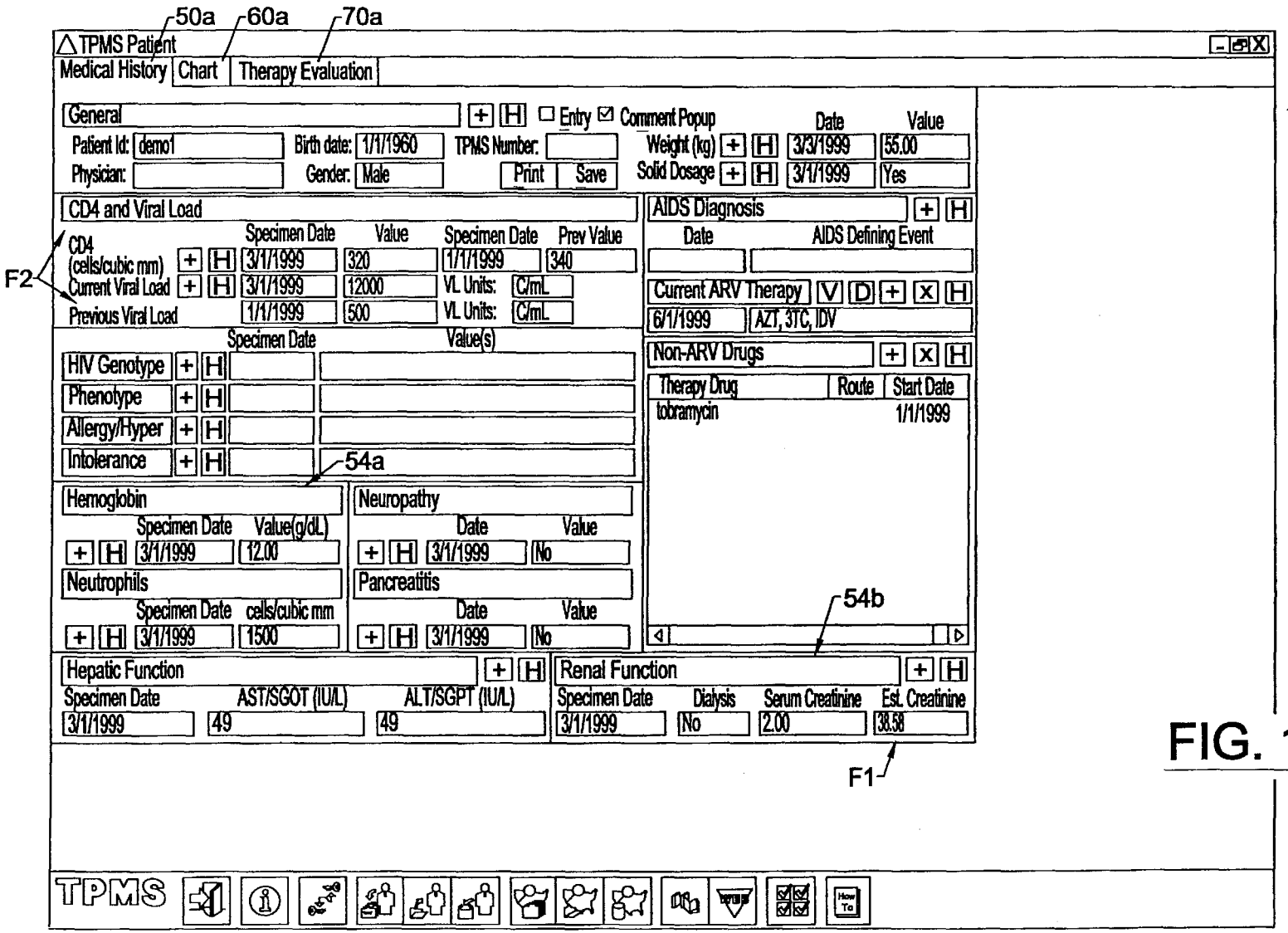

50a
60a
70a
50
TPMS Patient
Medical History
Chart
Therapy Evaluation
General
Entry
Comment Popup
Patient Id: demo1
Birth date: 1/1/1960
TPMS Number:
Physician:
Gender: Male
Print
Save
Weight (kg) 3/3/1999 55.00
Solid Dosage 3/1/1999 Yes
CD4 and Viral Load
CD4 (cells/cubic mm) 3/1/1999 320 1/1/1999 340
Current Viral Load 3/1/1999 12000 VL Units: C/mL
Previous Viral Load 1/1/1999 500 VL Units: C/mL
F2
AIDS Diagnosis
Current ARV Therapy
6/1/1999 AZT, 3TC, IDV
Non-ARV Drugs
Therapy Drug
Route
Start Date
tobramycin 1/1/1999
HIV Genotype
Phenotype
Allergy/Hyper
Intolerance
54a
Hemoglobin
3/1/1999 12.00
Neutrophils
3/1/1999 1500
Neuropathy
3/1/1999 No
Pancreatitis
3/1/1999 No
54b
Hepatic Function
3/1/1999 49 49
Renal Function
3/1/1999 No 2.00 38.58
F1
TPMS

FIG. 10A.

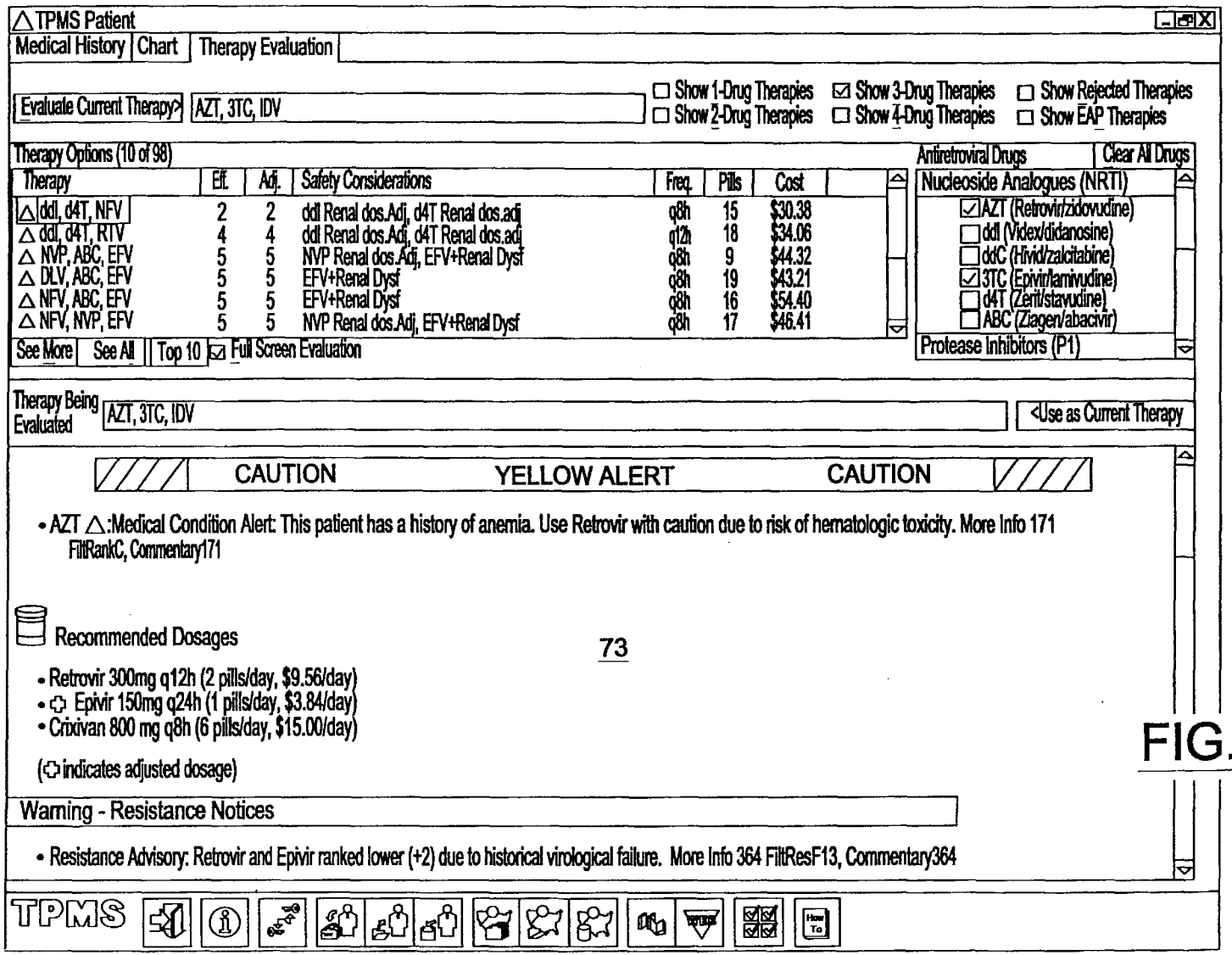

△TPMS Patient
Medical History
Chart
Therapy Evaluation
Evaluate Current Therapy>
AZT, 3TC, IDV
☐ Show 1-Drug Therapies
☐ Show 2-Drug Therapies
☑ Show 3-Drug Therapies
☐ Show 4-Drug Therapies
☐ Show Rejected Therapies
☐ Show EAP Therapies
70
Therapy Options (10 of 98)
Therapy | Eff. | Adj. | Safety Considerations | Freq. | Pills | Cost
△ddI, d4T, NFV | 2 | 2 | ddI Renal dos.Adj, d4T Renal dos.adj | q8h | 15 | $30.38
△ddI, d4T, RTV | 4 | 4 | ddI Renal dos.Adj, d4T Renal dos.adj | q12h | 18 | $34.06
△NVP, ABC, EFV | 5 | 5 | NVP Renal dos.Adj, EFV+Renal Dysf | q8h | 9 | $44.32
△DLV, ABC, EFV | 5 | 5 | EFV+Renal Dysf | q8h | 19 | $43.21
△NFV, ABC, EFV | 5 | 5 | EFV+Renal Dysf | q8h | 16 | $54.40
△NFV, NVP, EFV | 5 | 5 | NVP Renal dos.Adj, EFV+Renal Dysf | q8h | 17 | $46.41
See More
See All
Top 10
☑ Full Screen Evaluation
Antiretroviral Drugs
Clear All Drugs
Nucleoside Analogues (NRTI)
☑ AZT (Retrovir/zidovudine)
☐ ddI (Videx/didanosine)
☐ ddC (Hivid/zalcitabine)
☑ 3TC (Epivir/lamivudine)
☐ d4T (Zerit/stavudine)
☐ ABC (Ziagen/abacivir)
Protease Inhibitors (P1)
Therapy Being Evaluated
AZT, 3TC, IDV
<Use as Current Therapy
CAUTION YELLOW ALERT CAUTION
• AZT △:Medical Condition Alert: This patient has a history of anemia. Use Retrovir with caution due to risk of hematologic toxicity. More Info 171 FiltRankC, Commentary171
Recommended Dosages
73
• Retrovir 300mg q12h (2 pills/day, $9.56/day)
• ✣ Epivir 150mg q24h (1 pills/day, $3.84/day)
• Crixivan 800 mg q8h (6 pills/day, $15.00/day)
(✣ indicates adjusted dosage)
Warning - Resistance Notices
• Resistance Advisory: Retrovir and Epivir ranked lower (+2) due to historical virological failure. More Info 364 FiltResF13, Commentary364
TPMS

FIG. 10B.

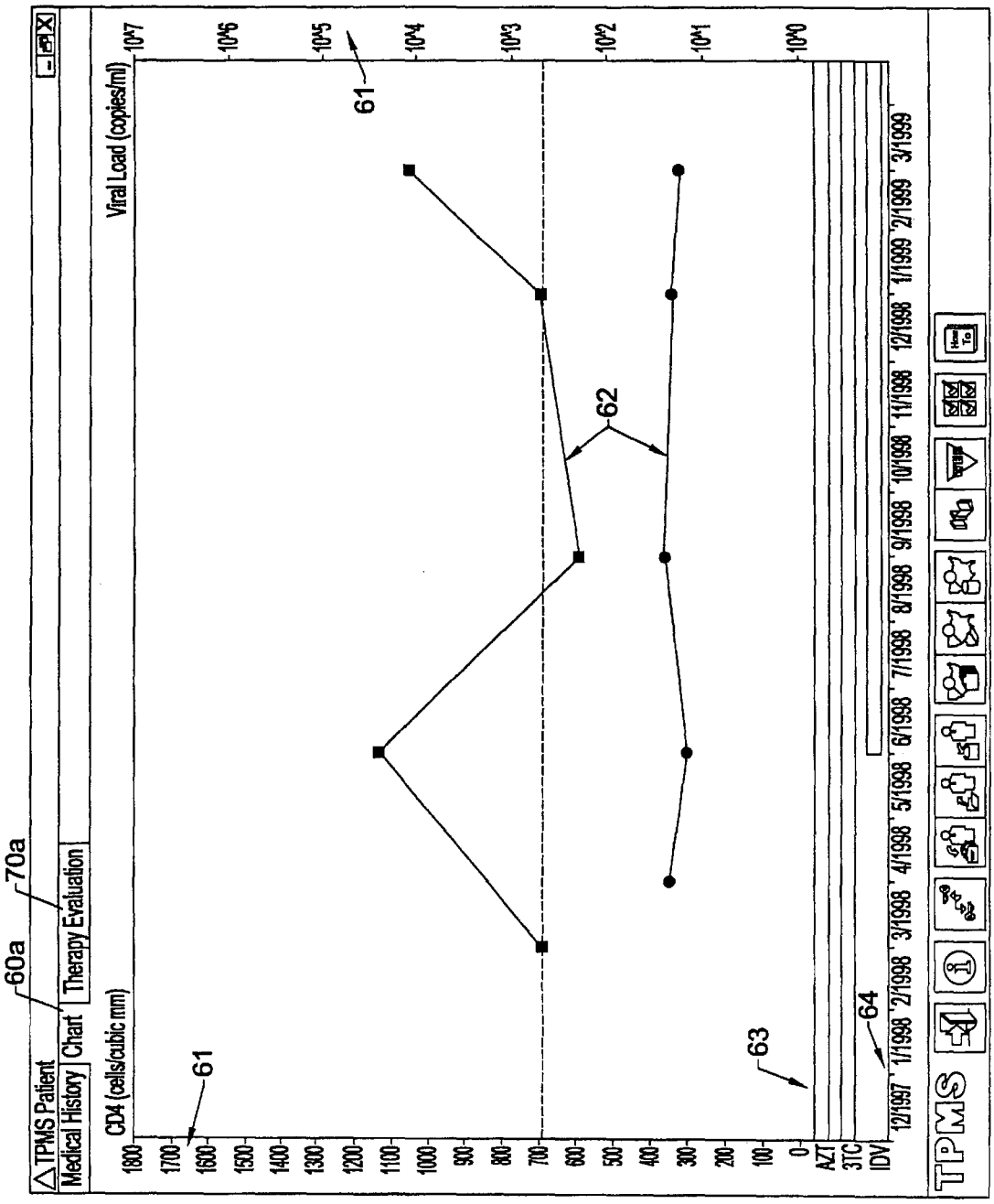

60
60a
70a
TPMS Patient
Medical History
Chart
Therapy Evaluation
CD4 (cells/cubic mm)
Viral Load (copies/ml)
61
62
63
64
AZT
3TC
IDV
TPMS

FIG. 10C.

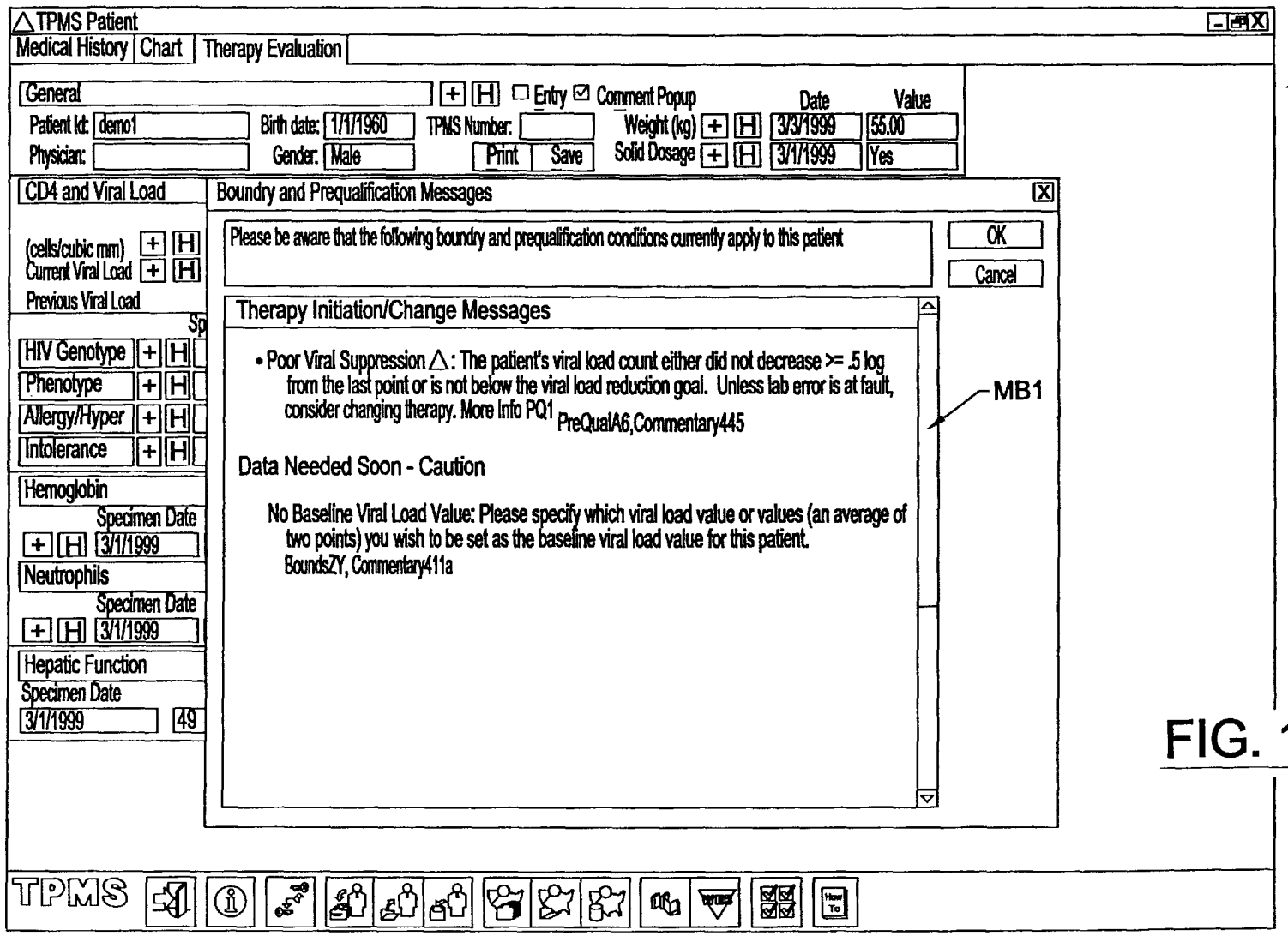

TPMS Patient
Medical History
Chart
Therapy Evaluation
General
Entry
Comment Popup
Date
Value
Patient Id: demo1
Birth date: 1/1/1960
TPMS Number:
Weight (kg) 3/3/1999 55.00
Physician:
Gender: Male
Print
Save
Solid Dosage 3/1/1999 Yes
CD4 and Viral Load
(cells/cubic mm)
Current Viral Load
Previous Viral Load
HIV Genotype
Phenotype
Allergy/Hyper
Intolerance
Hemoglobin
Specimen Date
3/1/1999
Neutrophils
Specimen Date
3/1/1999
Hepatic Function
Specimen Date
3/1/1999
49
Boundry and Prequalification Messages
Please be aware that the following boundry and prequalification conditions currently apply to this patient
OK
Cancel
Therapy Initiation/Change Messages
• Poor Viral Suppression △: The patient's viral load count either did not decrease >= .5 log from the last point or is not below the viral load reduction goal. Unless lab error is at fault, consider changing therapy. More Info PQ1 PreQualA6,Commentary445
Data Needed Soon - Caution
No Baseline Viral Load Value: Please specify which viral load value or values (an average of two points) you wish to be set as the baseline viral load value for this patient.
BoundsZY, Commentary411a
MB1
70
TPMS

FIG. 10D.

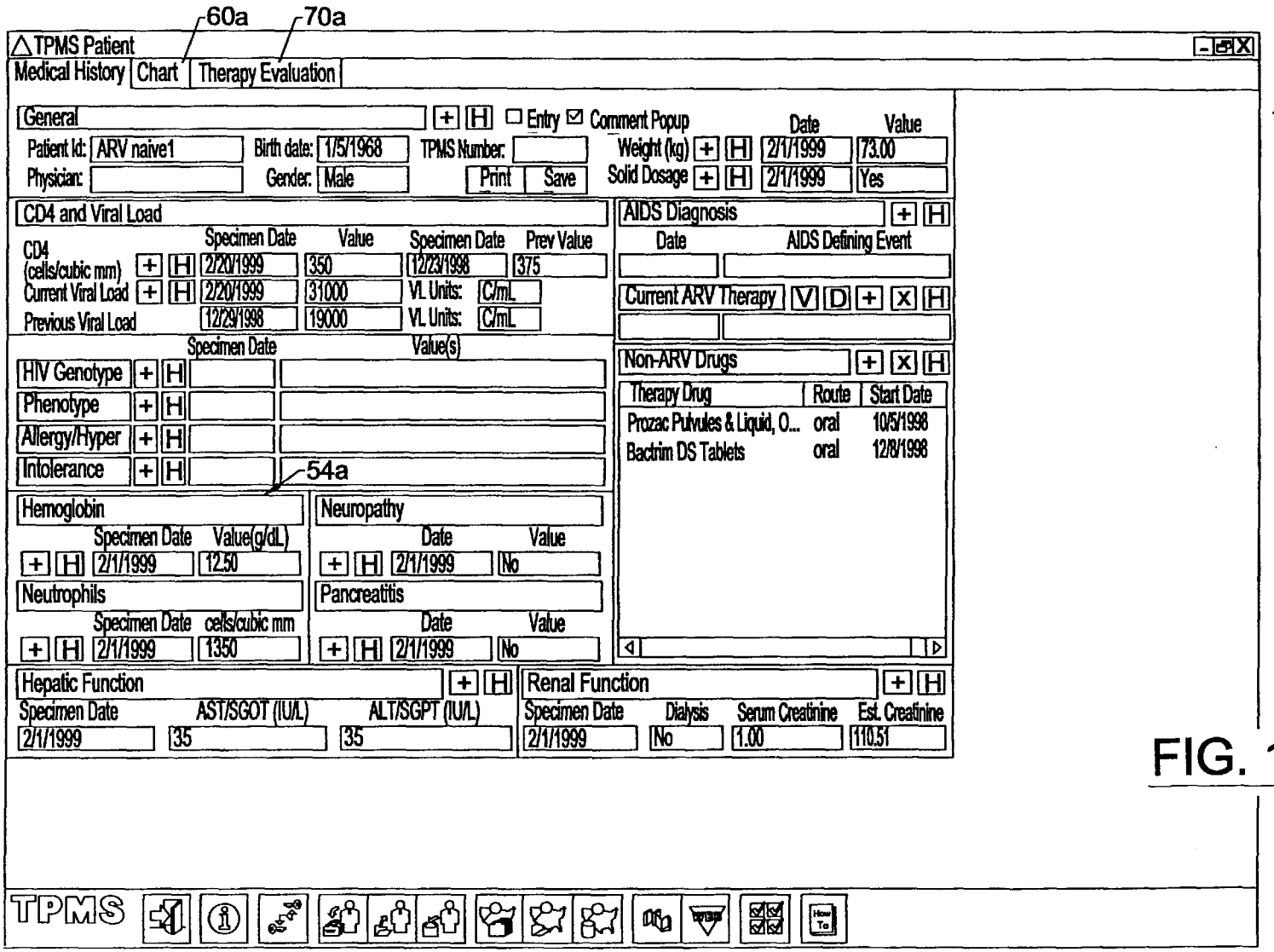

60a
70a
50
TPMS Patient
Medical History
Chart
Therapy Evaluation
General
Entry
Comment Popup
Patient Id: ARV naive1
Birth date: 1/5/1968
TPMS Number:
Physician:
Gender: Male
Print
Save
Weight (kg) 2/1/1999 73.00
Solid Dosage 2/1/1999 Yes
CD4 and Viral Load
CD4 (cells/cubic mm) 2/20/1999 350 12/23/1998 375
Current Viral Load 2/20/1999 31000 VL Units: C/mL
Previous Viral Load 12/29/1998 19000 VL Units: C/mL
HIV Genotype
Phenotype
Allergy/Hyper
Intolerance
54a
AIDS Diagnosis
Date
AIDS Defining Event
Current ARV Therapy
Non-ARV Drugs
Therapy Drug
Route
Start Date
Prozac Pulvules & Liquid, O... oral 10/5/1998
Bactrim DS Tablets oral 12/8/1998
Hemoglobin
Specimen Date
Value(g/dL)
2/1/1999 12.50
Neutrophils
Specimen Date
cells/cubic mm
2/1/1999 1350
Neuropathy
Date
Value
2/1/1999 No
Pancreatitis
Date
Value
2/1/1999 No
Hepatic Function
Specimen Date
AST/SGOT (IU/L)
ALT/SGPT (IU/L)
2/1/1999 35 35
Renal Function
Specimen Date
Dialysis
Serum Creatinine
Est. Creatinine
2/1/1999 No 1.00 110.51
TPMS

FIG. 11A.

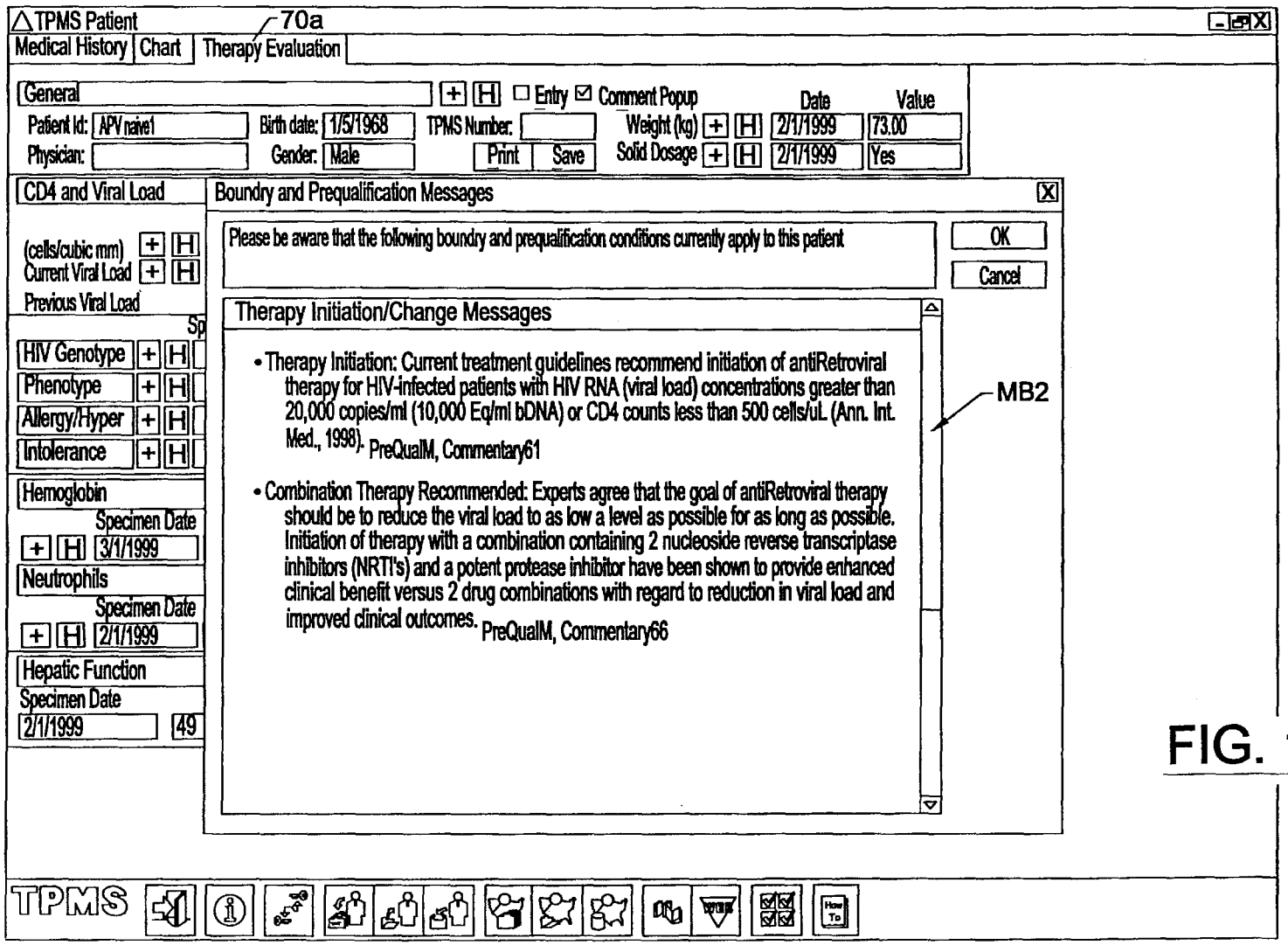

TPMS Patient
70a
Medical History
Chart
Therapy Evaluation
General
Entry
Comment Popup
Date
Value
Patient Id: APV naive1
Birth date: 1/5/1968
TPMS Number:
Weight (kg) 2/1/1999 73.00
Physician:
Gender: Male
Print
Save
Solid Dosage 2/1/1999 Yes
CD4 and Viral Load
(cells/cubic mm)
Current Viral Load
Previous Viral Load
HIV Genotype
Phenotype
Allergy/Hyper
Intolerance
Hemoglobin
Specimen Date
3/1/1999
Neutrophils
Specimen Date
2/1/1999
Hepatic Function
Specimen Date
2/1/1999
49
Boundry and Prequalification Messages
Please be aware that the following boundry and prequalification conditions currently apply to this patient
OK
Cancel
Therapy Initiation/Change Messages
• Therapy Initiation: Current treatment guidelines recommend initiation of antiRetroviral therapy for HIV-infected patients with HIV RNA (viral load) concentrations greater than 20,000 copies/ml (10,000 Eq/ml bDNA) or CD4 counts less than 500 cells/uL (Ann. Int. Med., 1998). PreQualM, Commentary61
• Combination Therapy Recommended: Experts agree that the goal of antiRetroviral therapy should be to reduce the viral load to as low a level as possible for as long as possible. Initiation of therapy with a combination containing 2 nucleoside reverse transcriptase inhibitors (NRTI's) and a potent protease inhibitor have been shown to provide enhanced clinical benefit versus 2 drug combinations with regard to reduction in viral load and improved clinical outcomes. PreQualM, Commentary66
MB2
70
TPMS

FIG. 11B.

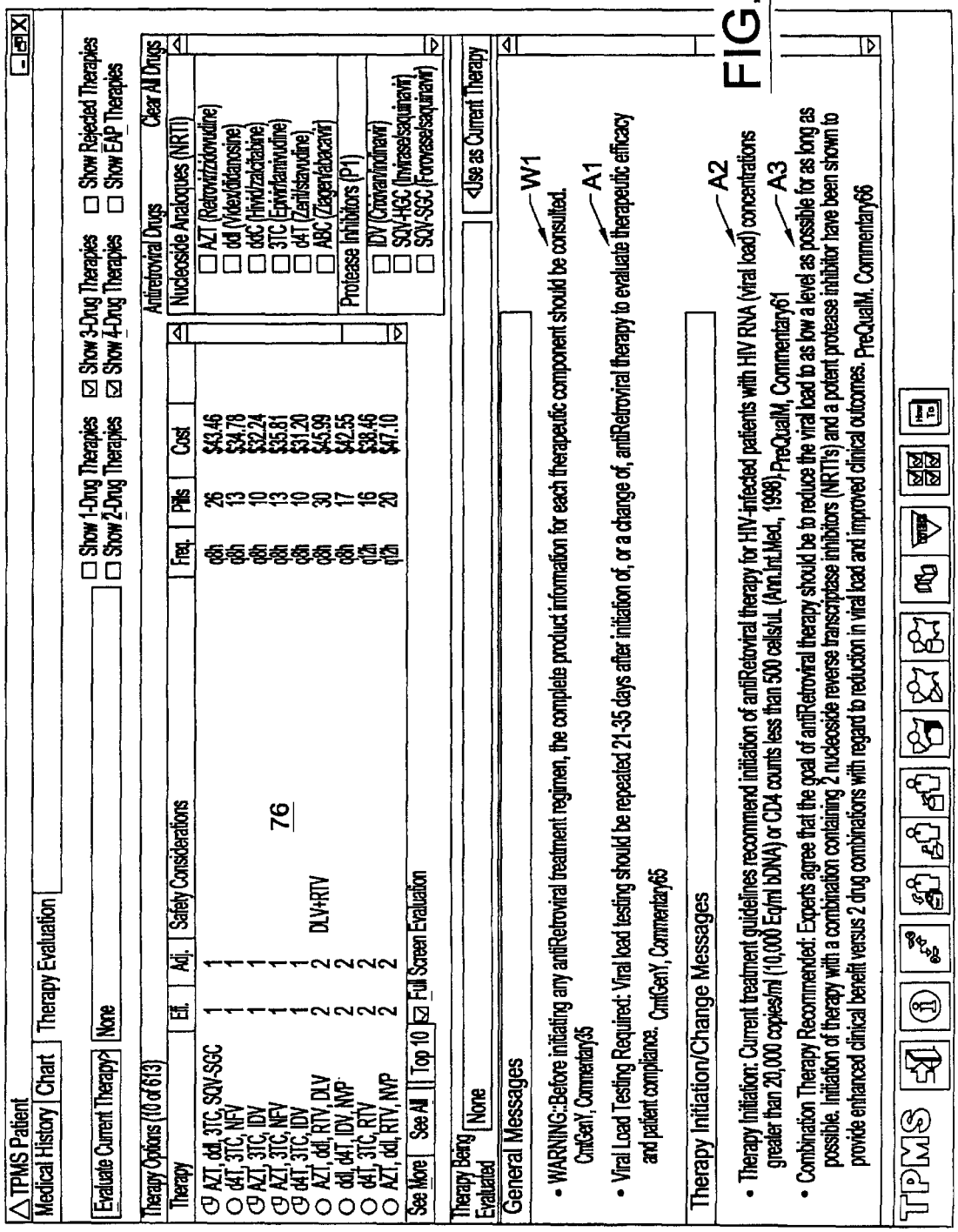

TPMS Patient
Medical History | Chart | Therapy Evaluation
Evaluate Current Therapy? None
Show 1-Drug Therapies
Show 2-Drug Therapies
Show 3-Drug Therapies
Show 4-Drug Therapies
Show Rejected Therapies
Show EAP Therapies
Therapy Options (10 of 613)
Antiretroviral Drugs
Clear All Drugs
Therapy
Eff.
Adj.
Safety Considerations
Freq.
Pills
Cost
AZT, ddI, 3TC, SQV-SGC
d4T, 3TC, NFV
AZT, 3TC, IDV
AZT, 3TC, NFV
d4T, 3TC, IDV
AZT, ddI, RTV, DLV
ddI, d4T, IDV, NVP
d4T, 3TC, RTV
AZT, ddI, RTV, NVP
DLV+RTV
76
q8h
q12h
$43.46
$34.78
$52.24
$35.81
$31.20
$45.99
$42.55
$38.46
$47.10
Nucleoside Analogues (NRTI)
AZT (Retrovir/zidovudine)
ddI (Videx/didanosine)
ddC (Hivid/zalcitabine)
3TC (Epivir/lamivudine)
d4T (Zerit/stavudine)
ABC (Ziagen/abacavir)
Protease Inhibitors (PI)
IDV (Crixivan/indinavir)
SQV-HGC (Invirase/saquinavir)
SQV-SGC (Fortovase/saquinavir)
See More
See All
Top 10
Full Screen Evaluation
Therapy Being Evaluated
None
Use as Current Therapy
General Messages
• WARNING::Before initiating any antiRetroviral treatment regimen, the complete product information for each therapeutic component should be consulted. CmtGenY, Commentary35
• Viral Load Testing Required: Viral load testing should be repeated 21-35 days after initiation of, or a change of, antiRetroviral therapy to evaluate therapeutic efficacy and patient compliance. CmtGenY, Commentary65
W1
A1
A2
A3
Therapy Initiation/Change Messages
• Therapy Initiation: Current treatment guidelines recommend initiation of antiRetroviral therapy for HIV-infected patients with HIV RNA (viral load) concentrations greater than 20,000 copies/ml (10,000 Eq/ml bDNA) or CD4 counts less than 500 cells/uL (Ann.Int.Med., 1998),PreQualM, Commentary61
• Combination Therapy Recommended: Experts agree that the goal of antiRetroviral therapy should be to reduce the viral load to as low a level as possible for as long as possible. Initiation of therapy with a combination containing 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a potent protease inhibitor have been shown to provide enhanced clinical benefit versus 2 drug combinations with regard to reduction in viral load and improved clinical outcomes. PreQualM, Commentary66
TPMS

FIG. 11C.

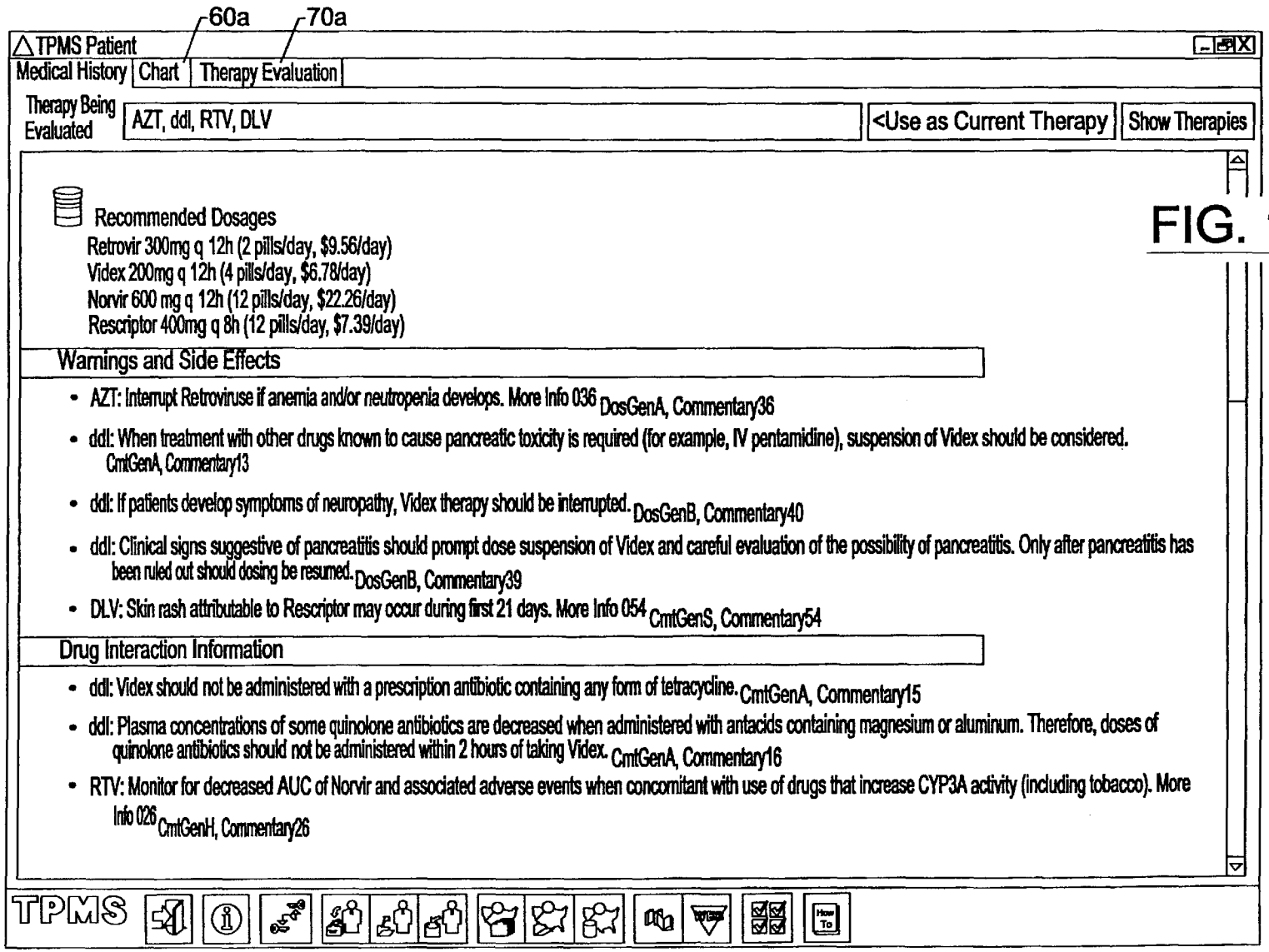

60a
70a
TPMS Patient
Medical History
Chart
Therapy Evaluation
Therapy Being Evaluated
AZT, ddI, RTV, DLV
<Use as Current Therapy
Show Therapies
Recommended Dosages
Retrovir 300mg q 12h (2 pills/day, $9.56/day)
Videx 200mg q 12h (4 pills/day, $6.78/day)
Norvir 600 mg q 12h (12 pills/day, $22.26/day)
Rescriptor 400mg q 8h (12 pills/day, $7.39/day)
Warnings and Side Effects
• AZT: Interrupt Retroviruse if anemia and/or neutropenia develops. More Info 036 DosGenA, Commentary36
• ddI: When treatment with other drugs known to cause pancreatic toxicity is required (for example, IV pentamidine), suspension of Videx should be considered. CmtGenA, Commentary13
• ddI: If patients develop symptoms of neuropathy, Videx therapy should be interrupted. DosGenB, Commentary40
• ddI: Clinical signs suggestive of pancreatitis should prompt dose suspension of Videx and careful evaluation of the possibility of pancreatitis. Only after pancreatitis has been ruled out should dosing be resumed. DosGenB, Commentary39
• DLV: Skin rash attributable to Rescriptor may occur during first 21 days. More Info 054 CmtGenS, Commentary54
Drug Interaction Information
• ddI: Videx should not be administered with a prescription antibiotic containing any form of tetracycline. CmtGenA, Commentary15
• ddI: Plasma concentrations of some quinolone antibiotics are decreased when administered with antacids containing magnesium or aluminum. Therefore, doses of quinolone antibiotics should not be administered within 2 hours of taking Videx. CmtGenA, Commentary16
• RTV: Monitor for decreased AUC of Norvir and associated adverse events when concomitant with use of drugs that increase CYP3A activity (including tobacco). More Info 026 CmtGenH, Commentary26
TPMS
How To

FIG. 11D.

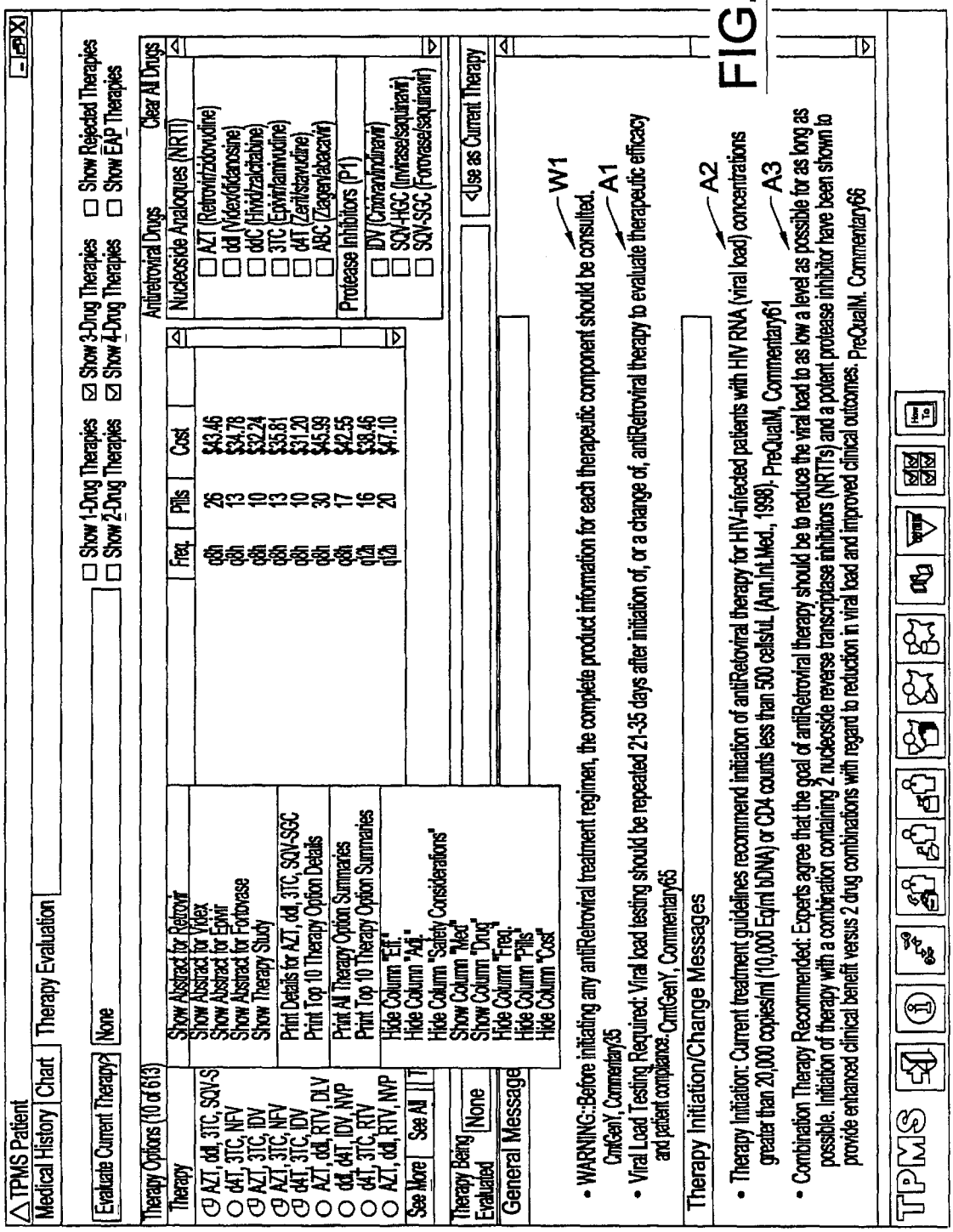

TPMS Patient
Medical History
Chart
Therapy Evaluation
Evaluate Current Therapy?
None
Show 1-Drug Therapies
Show 2-Drug Therapies
Show 3-Drug Therapies
Show 4-Drug Therapies
Show Rejected Therapies
Show EAP Therapies
Therapy Options (10 of 613)
Antiretroviral Drugs
Clear All Drugs
Therapy
Freq
Pills
Cost
Nucleoside Analogues (NRTI)
AZT (Retrovir/zidovudine)
ddI (Videx/didanosine)
ddC (Hivid/zalcitabine)
3TC (Epivir/lamivudine)
d4T (Zerit/stavudine)
ABC (Ziagen/abacavir)
Protease Inhibitors (PI)
IDV (Crixivan/indinavir)
SQV-HGC (Invirase/saquinavir)
SQV-SGC (Fortovase/saquinavir)
Show Abstract for Retrovir
Show Abstract for Videx
Show Abstract for Epivir
Show Abstract for Fortovase
Show Therapy Study
Print Details for AZT, ddI, 3TC, SQV-SGC
Print Top 10 Therapy Option Details
Print All Therapy Option Summaries
Print Top 10 Therapy Option Summaries
Hide Column "Eff."
Hide Column "Adj."
Hide Column "Safety Considerations"
Show Column "Med"
Show Column "Drug"
Hide Column "Freq"
Hide Column "Pills"
Hide Column "Cost"
AZT, ddI, 3TC, SQV-S
d4T, 3TC, NFV
AZT, 3TC, IDV
AZT, 3TC, NFV
d4T, 3TC, IDV
AZT, ddI, RTV, DLV
ddI, d4T, IDV, NVP
d4T, 3TC, RTV
AZT, ddI, RTV, NVP
q8h 26 $43.46
q8h 13 $34.78
q8h 10 $32.24
q8h 13 $35.81
q8h 10 $31.20
q8h 30 $45.99
q8h 17 $42.55
q12h 16 $38.46
q12h 20 $47.10
See More
See All
Therapy Being Evaluated
None
Use as Current Therapy
General Message
W1
• WARNING:: Before initiating any antiRetroviral treatment regimen, the complete product information for each therapeutic component should be consulted. CmtGenY, Commentary35
A1
• Viral Load Testing Required: Viral load testing should be repeated 21-35 days after initiation of, or a change of, antiRetroviral therapy to evaluate therapeutic efficacy and patient compliance. CmtGenY, Commentary65
A2
Therapy Initiation/Change Messages
• Therapy Initiation: Current treatment guidelines recommend initiation of antiRetroviral therapy for HIV-infected patients with HIV RNA (viral load) concentrations greater than 20,000 copies/ml (10,000 Eq/ml bDNA) or CD4 counts less than 500 cells/uL (Ann.Int.Med., 1998). PreQualM, Commentary61
A3
• Combination Therapy Recommended: Experts agree that the goal of antiRetroviral therapy should be to reduce the viral load to as low a level as possible for as long as possible. Initiation of therapy with a combination containing 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a potent protease inhibitor have been shown to provide enhanced clinical benefit versus 2 drug combinations with regard to reduction in viral load and improved clinical outcomes. PreQualM, Commentary66
TPMS

FIG. 11E.

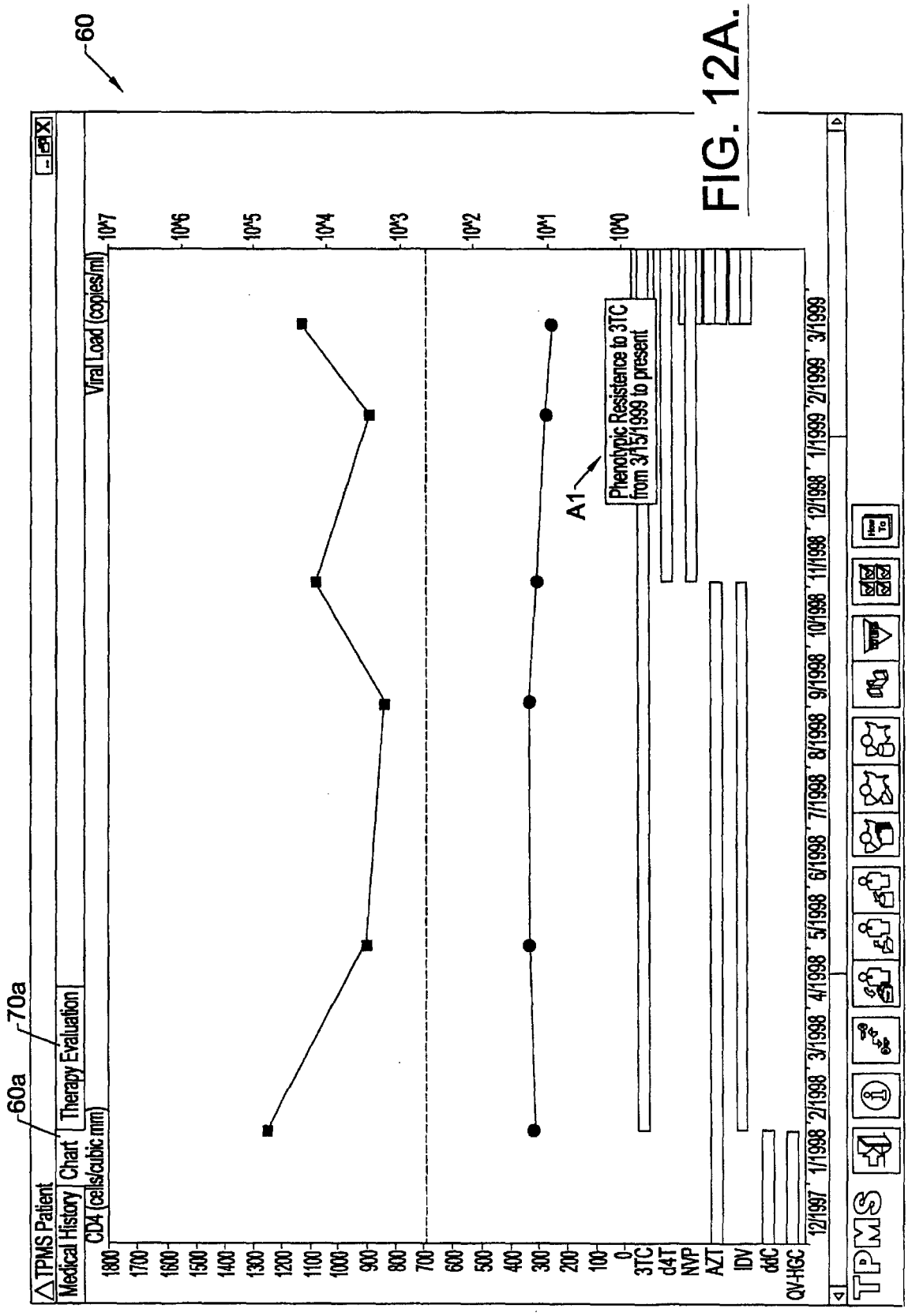

60
70a
60a
TPMS Patient
Medical History
Chart
Therapy Evaluation
CD4 (cells/cubic mm)
Viral Load (copies/ml)
Phenotypic Resistance to 3TC from 3/15/1999 to present
A1
3TC
d4T
NVP
AZT
IDV
ddC
QV-HGC
12/1997
1/1998
2/1998
3/1998
4/1998
5/1998
6/1998
7/1998
8/1998
9/1998
10/1998
11/1998
12/1998
1/1999
2/1999
3/1999
TPMS

FIG. 12A.

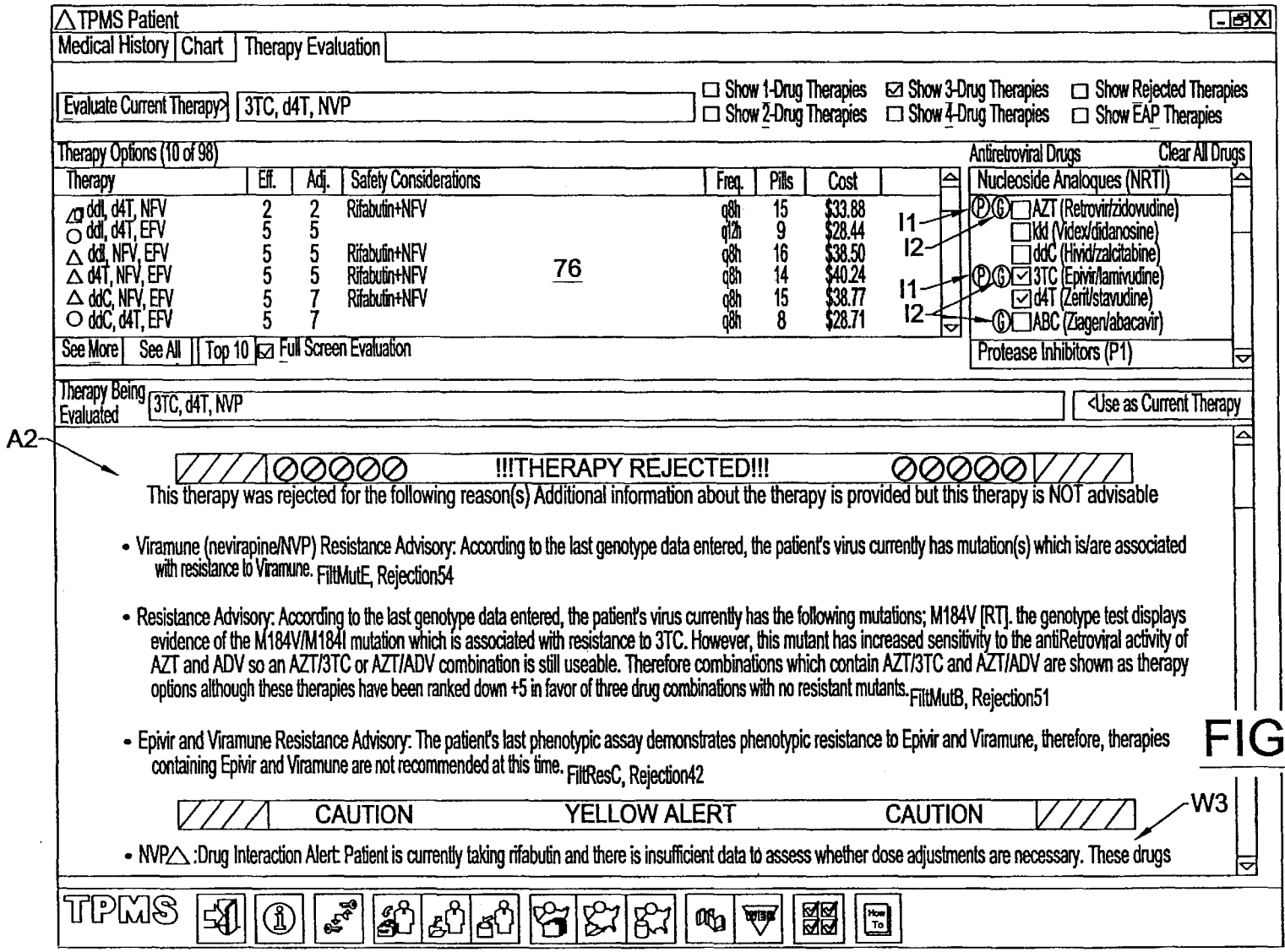

TPMS Patient
Medical History
Chart
Therapy Evaluation
Evaluate Current Therapy>
3TC, d4T, NVP
Show 1-Drug Therapies
Show 3-Drug Therapies
Show Rejected Therapies
Show 2-Drug Therapies
Show 4-Drug Therapies
Show EAP Therapies
Therapy Options (10 of 98)
Antiretroviral Drugs
Clear All Drugs
Therapy
Eff.
Adj.
Safety Considerations
Freq.
Pills
Cost
ddI, d4T, NFV 2 2 Rifabutin+NFV q8h 15 $33.88
ddI, d4T, EFV 5 5 q12h 9 $28.44
ddI, NFV, EFV 5 5 Rifabutin+NFV q8h 16 $38.50
d4T, NFV, EFV 5 5 Rifabutin+NFV q8h 14 $40.24
ddC, NFV, EFV 5 7 Rifabutin+NFV q8h 15 $38.77
ddC, d4T, EFV 5 7 q8h 8 $28.71
76
I1
I2
I1
I2
Nucleoside Analoques (NRTI)
AZT (Retrovir/zidovudine)
ddI (Videx/didanosine)
ddC (Hivid/zalcitabine)
3TC (Epivir/lamivudine)
d4T (Zerit/stavudine)
ABC (Ziagen/abacavir)
Protease Inhibitors (P1)
See More
See All
Top 10
Full Screen Evaluation
Therapy Being Evaluated
3TC, d4T, NVP
<Use as Current Therapy
A2
!!!THERAPY REJECTED!!!
This therapy was rejected for the following reason(s) Additional information about the therapy is provided but this therapy is NOT advisable
• Viramune (nevirapine/NVP) Resistance Advisory: According to the last genotype data entered, the patient's virus currently has mutation(s) which is/are associated with resistance to Viramune. FiltMutE, Rejection54
• Resistance Advisory: According to the last genotype data entered, the patient's virus currently has the following mutations; M184V [RT]. the genotype test displays evidence of the M184V/M184I mutation which is associated with resistance to 3TC. However, this mutant has increased sensitivity to the antiRetroviral activity of AZT and ADV so an AZT/3TC or AZT/ADV combination is still useable. Therefore combinations which contain AZT/3TC and AZT/ADV are shown as therapy options although these therapies have been ranked down +5 in favor of three drug combinations with no resistant mutants. FiltMutB, Rejection51
• Epivir and Viramune Resistance Advisory: The patient's last phenotypic assay demonstrates phenotypic resistance to Epivir and Viramune, therefore, therapies containing Epivir and Viramune are not recommended at this time. FiltResC, Rejection42
CAUTION YELLOW ALERT CAUTION
W3
• NVP△:Drug Interaction Alert: Patient is currently taking rifabutin and there is insufficient data to assess whether dose adjustments are necessary. These drugs
TPMS

FIG. 12B.

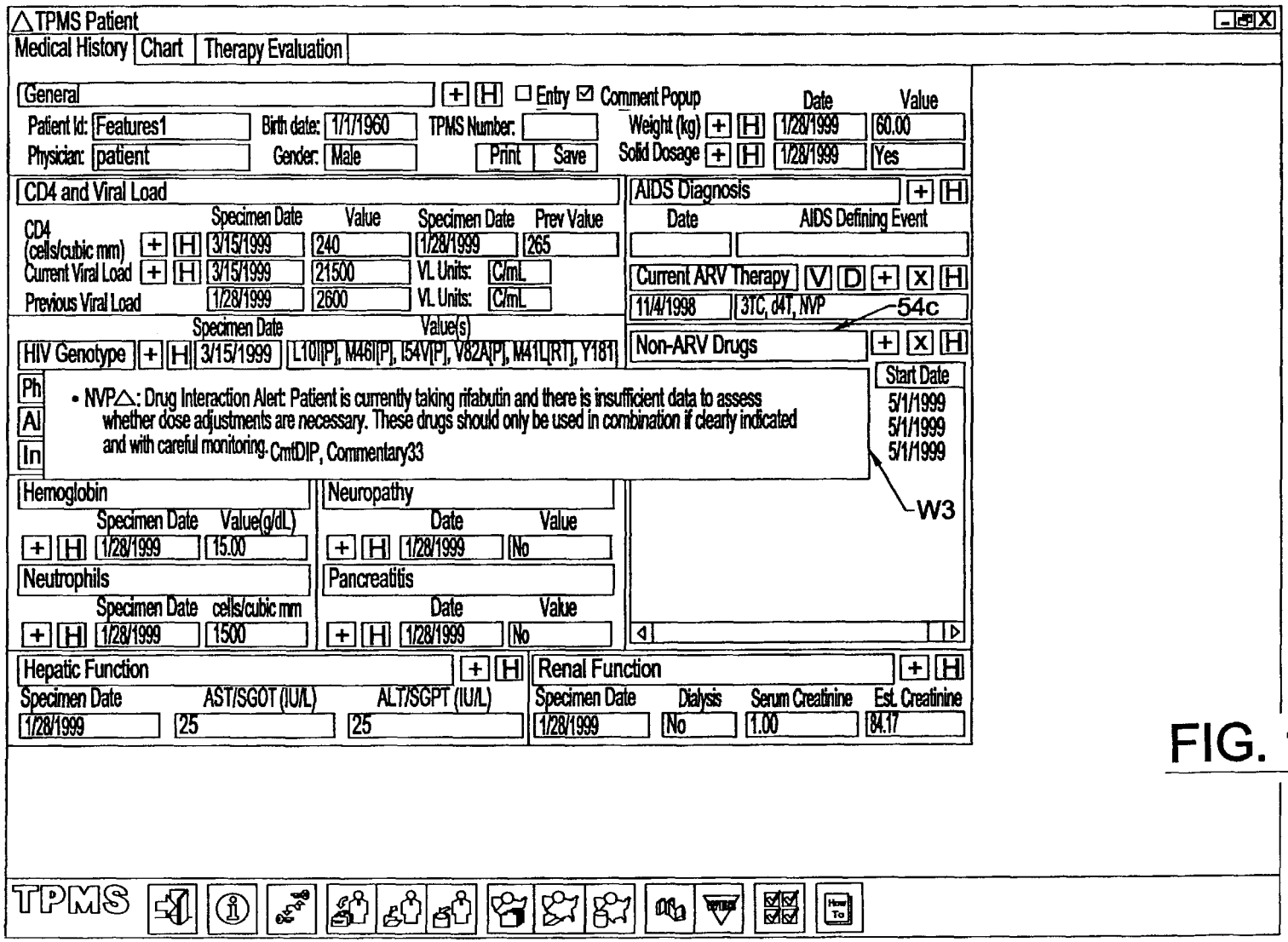

△TPMS Patient
Medical History
Chart
Therapy Evaluation
General
Entry
Comment Popup
Patient Id: Features1
Birth date: 1/1/1960
TPMS Number:
Physician: patient
Gender: Male
Print
Save
Weight (kg) 1/28/1999 60.00
Solid Dosage 1/28/1999 Yes
CD4 and Viral Load
CD4 (cells/cubic mm) 3/15/1999 240 1/28/1999 265
Current Viral Load 3/15/1999 21500 VL Units: C/mL
Previous Viral Load 1/28/1999 2600 VL Units: C/mL
HIV Genotype 3/15/1999 L10I[P], M46I[P], I54V[P], V82A[P], M41L[RT], Y181
AIDS Diagnosis
Date
AIDS Defining Event
Current ARV Therapy
11/4/1998 3TC, d4T, NVP
54c
Non-ARV Drugs
Start Date
5/1/1999
5/1/1999
5/1/1999
• NVP△: Drug Interaction Alert: Patient is currently taking rifabutin and there is insufficient data to assess whether dose adjustments are necessary. These drugs should only be used in combination if clearly indicated and with careful monitoring. CmtDIP, Commentary33
W3
Hemoglobin
Specimen Date Value(g/dL)
1/28/1999 15.00
Neutrophils
Specimen Date cells/cubic mm
1/28/1999 1500
Neuropathy
Date Value
1/28/1999 No
Pancreatitis
Date Value
1/28/1999 No
Hepatic Function
Specimen Date AST/SGOT (IU/L) ALT/SGPT (IU/L)
1/28/1999 25 25
Renal Function
Specimen Date Dialysis Serum Creatinine Est. Creatinine
1/28/1999 No 1.00 84.17
TPMS

FIG. 12C.

SYSTEMS, METHODS AND COMPUTER PROGRAM PRODUCTS FOR GUIDING THE SELECTION OF THERAPEUTIC TREATMENT REGIMENS

RELATED APPLICATIONS

This application is a continuation of copending application Ser. No. 09/283,702, filed Apr. 1, 1999, which claims priority from provisional application Ser. No. 60/080,629, filed Apr. 3, 1998, the disclosure of both of which are incorporated by reference herein in their entirety.

A portion of the disclosure of this patent document contains material that is the subject of copyright protection. The copyright owner does not object to the reproduction of the patent disclosure as it appears in the public patent files of the Unites States Patent and Trademark Office, but otherwise reserves all other rights in the copyrighted material.

FIELD OF THE INVENTION

This invention concerns systems, methods and computer program products for guiding the selection of therapeutic treatment regimens for complex disorders such as cancer and HIV-1 infection, wherein a ranking of available treatment regimens is generated and advisory information clinically useful for treating patients is provided.

BACKGROUND OF THE INVENTION

Therapeutic treatment regimens for disorders such as HIV-1 infection (acquired immune deficiency syndrome or AIDS) and cancer are increasingly complex. New data and new therapeutic treatment regimens continue to modify the treatments available, and it is difficult for all but the specialist to remain current on the latest treatment information. Further, even those who are current on the latest treatment information require time to assimilate that information and understand how it relates to other treatment information in order to provide the best available treatment for a patient. Combination therapeutic treatment regimens exacerbate this problem by making potential drug interactions even more complex. Finally, an increasingly sophisticated patient population, in the face of a vast volume of consumer information on the treatment of disease, makes the mere statement of a treatment regime, without explanation, difficult for the patient to accept.

R. Miller et al., Summary Recommendations for Responsible Monitoring and Regulation of Clinical Software Systems, Ann. Intern. Med. 127, 842–845 (1997), describes policy guidelines indicating the desirability of systems that generate advice for clinician users in a manner that users can easily override. Solutions to this need are neither suggested nor disclosed.

M. Pazzani et al., Application of an Expert System in the Management of HIV-Infected Patients, J. Acquired Immune Deficiency Syndromes and Human Retrovirology 15, 356–362 (1997)(accepted May 12, 1997), describes a rule-based expert system by which protease, reverse transcriptase, and integrase segments of HIV are cloned and entered into an expert system that recommends two, three, and four drug regimens. A means for easily overriding the advice given is neither suggested nor disclosed.

U.S. Pat. No. 5,672,154 to Sillen describes a method for giving patients individualized, situation dependent medication advice. The recommended type of medicine may include at least two different medicines. No means for ranking multiple treatment options is disclosed, and no means for explaining why treatment options were rejected is given. Rather, this system is primarily concerned with generating new rules from patient information to optimize a particular therapy for diseases such as Parkinson's disease, epilepsy and abnormal blood pressure.

U.S. Pat. No. 5,694,950 to McMichael describes a method and system for use in treating a patient with immunosuppressants such as cyclosporin. An expert system is employed to generate a recommendation on whether the immunosuppressant dosage should be changed and, if so, how. Ranking or selection among a plurality of different combination therapeutic treatment regimens is not suggested.

U.S. Pat. No. 5,594,638 to Iliff describes a medical diagnostic system that provides medical advice to the general public over a telephone network. This system is not concerned with generating a recommendation for a combination therapeutic treatment regimen for a known disease (see also U.S. Pat. No. 5,660,176 to Iliff).

SUMMARY OF THE INVENTION

In view of the foregoing, an object of the invention is to provide systems, methods and computer program products for selecting therapeutic treatment regimens for patients in which available treatments are listed, and optionally ranked, while unavailable or rejected treatment regimens (e.g., regimens that would not be effective, or would be dangerous) are not displayed or are assigned a low rank and are indicated to a user as not likely to be efficacious, or not preferred due to patient-specific complicating factors such as drug interaction from concomitant medications.

A further object of the invention is to provide systems, methods and computer program products for selecting treatment regimens in which the available treatment options can be readily understood.

A further object of the invention is to provide systems, methods and computer program products for selecting treatment regimens in which the implications of selecting a particular treatment regimen can be readily understood.

A further object of the invention is to provide systems, methods and computer program products for selecting treatment regimens in which the reasons for rejection of a particular regimen can be readily understood.

A still further object of the invention is to provide systems, methods and computer program products for obtaining information about the efficacy of previous treatment regimens imposed on patients.

A method of the present invention includes providing patient information to a computing device that includes various knowledge bases. For example, a first knowledge base may include a plurality of different therapeutic treatment regimens for a disease or medical condition. A second knowledge base may include a plurality of expert rules for selecting a therapeutic treatment regimen for the disease or medical condition. A third knowledge base may include advisory information useful for the treatment of a patient with different constituents of different therapeutic treatment regimens. A fourth knowledge base may include information about past therapies, such as how a patient has fared under previous therapies.

A listing (preferably a ranked listing) of therapeutic treatment regimens for a patient is generated in the computing device. Advisory information for one or more treatment regimens in the listing is generated in the computing device based on the patient information and the expert rules.

In a preferred embodiment, the method described above further includes entering a user-defined therapeutic treatment regimen for the disease (or medical condition) that may not be displayed from the system knowledge base-generated therapeutic treatment regimens, and generating in the computing device advisory information for the user-defined combination therapeutic treatment regimen.

In addition, in a preferred embodiment, the method described above further includes entering a rejected therapeutic treatment regimen for the disease (or medical condition) that is included in the first knowledge base but not recommended from the ranking (or given a very low ranking), and generating in the computing device advisory information for the non-recommended/low ranked therapeutic treatment regimen, wherein the advisory information includes at least one reason for not recommending (or low ranking) the therapeutic treatment regimen.

Further objects and aspects of the present invention are explained in detail in the drawings herein and the specification set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of the specification, illustrate embodiments of the invention and, together with the description, serve to explain principles of the invention.

FIG. **1** illustrates a process of the instant invention, including routines for entering a user-defined therapeutic treatment regimen and for entering a "non-recommended" therapeutic treatment regimen.

FIG. **2** schematically illustrates a system or apparatus of the present invention.

FIG. **3** illustrates a client-server environment within which the system of FIG. **2** may operate, according to an embodiment of the present invention, and wherein a central server is accessible by at least one local server via a computer network, such as the Internet, and wherein each local server is accessible by at least one client.

FIG. **4** illustrates a medical history user interface for entering data about a patient's medical history according to the present invention.

FIG. **5** illustrate a user interface chart for monitoring a patient's condition during a particular therapeutic treatment regimen over a period of time according to the present invention.

FIG. **6** illustrates a therapy evaluation user interface that facilitates evaluation of various therapeutic treatment regimen options with respect to relative efficacy, individualized adjusted relative efficacy, dosage, frequency, cost, medical complications and drug interactions according to the present invention.

FIG. **7** illustrates various symbols for providing information about a therapeutic treatment regimen option within the therapy list box of the therapy evaluation user interface of FIG. **6** according to the present invention.

FIG. **8** illustrates the therapy details box of FIG. **6** in "full screen" mode.

FIG. **9** illustrates a pop-up menu including an indexed electronic link to a PDR® that can be activated from within the therapy list box of the therapy evaluation user interface of FIG. **6** according to the present invention.

FIGS. **10**A–**10**D illustrate various functions of the present invention as described in Example 1.

FIGS. **11**A–**11**E illustrate various functions of the present invention as described in Example 2.

FIGS. **12**A–**12**C illustrate various functions of the present invention as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. Like numbers refer to like elements throughout.

As will be appreciated by one of skill in the art, the present invention may be embodied as a method, data processing system, or computer program product. Accordingly, the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment, or an embodiment combining software and hardware aspects. Furthermore, the present invention may take the form of a computer program product on a computer-usable storage medium having computer readable program code means embodied in the medium. Any suitable computer readable medium may be utilized including, but not limited to, hard disks, CD-ROMs, optical storage devices, and magnetic storage devices.

The present invention is described below with reference to flowchart illustrations of methods, apparatus (systems), and computer program products according to an embodiment of the invention. It will be understood that each block of the flowchart illustrations, and combinations of blocks in the flowchart illustrations, can be implemented by computer program instructions. These computer program instructions may be provided to a processor of a general purpose computer, special purpose computer, or other programmable data processing apparatus to produce a machine, such that the instructions, which execute via the processor of the computer or other programmable data processing apparatus, create means for implementing the functions specified in the flowchart block or blocks.

These computer program instructions may also be stored in a computer-readable memory that can direct a computer or other programmable data processing apparatus to function in a particular manner, such that the instructions stored in the computer-readable memory produce an article of manufacture including instruction means which implement the function specified in the flowchart block or blocks.

The computer program instructions may also be loaded onto a computer or other programmable data processing apparatus to cause a series of operational steps to be performed on the computer or other programmable apparatus to produce a computer implemented process such that the instructions which execute on the computer or other programmable apparatus provide steps for implementing the functions specified in the flowchart block or blocks.

A method of the instant invention is illustrated in FIG. **1**. In the first step **10**, the patient is examined to determine patient information. Examples of patient information that may be gathered include one or more of gender, age, weight, $CD4^+$ cell information, viral load information, HIV genotype and phenotype information, hemoglobin information, neuropathy information, neutrophil information, pancreatitis, hepatic function, renal function, drug allergy and intolerance information, and information for drug treat-

ments for other conditions. The information may include historical information on prior therapeutic treatment regimens for the disease or medical condition. While the patient is typically examined on a first visit to determine the patient information, it will be appreciated that patient information may also be stored in the computing device, or transferred to the computing device from another computing device, storage device, or hard copy, when the information has been previously determined.

The patient information is then provided **11** to a computing device that contains a knowledge base of treatments, contains a knowledge base of expert rules for determining available treatment options for the patient in light of the patient information, and also contains a knowledge base of advisory information. A list of available treatments for the patient is then generated **12** from the patient information and the available treatments by the expert rules, and advisory information for the available treatments is generated **13**. The advisory information may include warnings to take the patient off a contraindicated drug or select a suitable non contraindicated drug to treat the condition before initiating a corresponding treatment regimen and/or information clinically useful to implement a corresponding therapeutic treatment regimen.

For example, when the known disease is HIV-1 infection, the treatment regimen includes antiretroviral drugs, and the treatment regimen or advisory information may also include contraindicated or potentially adversely interacting non-antiretroviral drugs. Particularly, when the treatment regimen includes a protease inhibitor. A contraindicated drug may be terfenadine. When the treatment regimen includes indinavir, a contraindicated drug is cisapride.

Exemplary antiretroviral drugs are listed below in Table 1.

TABLE 1

Abbreviation	Formal Name	Generic Name
ABC	ZIAGEN ®	Abacavir
ADV	PREVEON ®	Adefovir
APV	AGENERASE ®	Amprenavir
AZT	RETROVIR ®	Zidovudine
ddI	VIDEX ®	Didanosine
ddC	HIVID ®	Zalcitabine
d4T	ZERIT ®	Stavudine
EFV	SUSTIVA ®	Efavirenz
3TC	EPIVIR ®	Lamivudine
SQV	INVIRASE ®/ FORTOVASE ®	Saquinavir
IDV	CRIXIVAN ®	Indinavir
RTV	NORVIR ®	Ritonavir
DLV	RESCRIPTOR ®	Delavirdine
NFV	VIRACEPT ®	Nelfinavir
NVP	VIRAMUNE ®	Nevirapine

Exemplary advisory information that can be displayed to a user is summarized below in Table 2.

TABLE 2

	Description
Drug Therapies (All the output data types below are associated with a therapy)	The inference engine will process every therapy from a resource file which contains all valid therapy combinations. The system will support multiple drug combinations. Those therapies which are recommended by the knowledge base will be displayed along with all the data types below.

TABLE 2-continued

	Description
Commentaries	Commentaries consist of warnings and advisories concerning drugs as well as various patient conditions. Each commentary will appear in specific locations of the User Interface. Commentaries will have various Flags, Triggers, and Output Locations.
Rejection Notices	Rejection Notices are the explanation why a given therapy is not recommended. Rejection notices always appear in predefined places in the User Interface.
Cost	The cost per day is calculated for each therapy by the inference engine as well as each drug cost within a therapy.
Dosage	The base dosage and any adjustments to the base dosage due to various patient conditions are calculated by the inference engine.
Pill Burden	The number of pills in the therapy.
Frequency	Number of times the patient will be taking medications for a given therapy. For a multi-drug therapy, the Frequency of the therapy is the drug in the therapy that has the highest number of Frequencies. If a three-drug regimen has 2 drugs with q12h dosages and one that is a q8h, the therapy is considered to be a q8h Frequency.
Admin	Special drug administration instructions.
Efficacy	The relative Efficacy is a whole number that represents the relative efficacy of the various therapies. One is the most effective therapy.
Adjusted Score	The "Adjusted Score" is the Efficacy adjusted up or down based on patient specific characteristics to roughly indicate the likelihood of that therapy being an effective treatment for that patient. An example would be: the system evaluates a therapy containing a drug that is known to be associated with a medical condition in that patient's medical history, therefore the therapy is ranked low. The Ranking Ordinal is an integer, beginning with 0 and having no upper limit. A therapy with a 1 Ranking Ordinal (RO = 1) would be ranked at the top of the list whereas a therapy with a 10 Ranking Ordinal (RO = 10) would be less likely to be successful given the patient's specific history and characteristics. Each therapy will have a starting RO number which will be the therapy's relative efficacy score. The relative efficacy score can then be adjusted up or down by the rules. Both base "Efficacy" number and the "Adjusted Score" number can be displayed.

Diseases (or medical conditions), the treatment of which may be facilitated or improved by the present invention, are those for which multiple different therapy options are available for selection and treatment. Such diseases and medical conditions include, but are not limited to, cardiovascular disease (including but not limited to congestive heart failure, hypertension, hyperlipidemia and angina), pulmonary disease (including but not limited to chronic obstructive pulmonary disease, asthma, pneumonia, cystic fibrosis, and tuberculosis), neurologic disease (including but not limited to Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis or ALS, psychoses such as schizophrenia and organic brain syndrome, neuroses, including anxiety, depression and bipolar disorder), hepatitis infections (including hepatitis B and hepatitis C infection), urinary tract infections, venereal disease, cancer (including but not limited to breast, lung, prostate, and colon cancer), etc. It should be appreciated that prevention of development or onset of the above-mentioned diseases and medical conditions may be facilitated or improved by the present invention.

The present invention is useful for known diseases such as HIV-1 infection (acquired immune deficiency syndrome or "AIDS"), or where the known disease is any medical condition for which a combination therapeutic treatment regimen can be used. The invention is particularly useful when the list of available treatments includes a plurality (e.g., 2, 10

or 15 or more) of treatment, combination therapeutic treatment regimens (e.g., therapeutic treatment regimens incorporating two or more active therapeutic agents), where the potential for drug interactions is increased and/or the complexity involved in selecting the best available treatment is multifactorial.

Advantageously, the list of available treatments and advisory information may be regenerated in a number of ways. The patient information may be simply modified **18**. In addition, if a particular therapy in which the user might be interested is not presented, a user-defined therapy may be entered **14** and advisory information generated **15** based on the user-defined therapy. Still further, if a therapeutic treatment regimen that is in the knowledge base is rejected by the system (not recommended upon display), the non-recommended therapeutic treatment regimen may be entered **16** and advisory information generated **17** for the non-recommended therapeutic treatment regimen. This may indicate to the user that they should discontinue use of a non-critical drug for another condition or select a suitable substitute that does not create a conflict/non-recommended situation so that they can then proceed with the therapy of choice. Alternatively, the advisory information can be generated automatically for non-recommended therapeutic treatment regimens. These various steps can be repeated in any sequence in an interactive manner to provide the user with assurance that all treatment options have been given adequate and appropriate consideration.

The terms "therapy" and "therapeutic treatment regimen" are interchangeable herein and, as used herein, mean any pharmaceutical or drug therapy, regardless of the route of delivery (e.g., oral, intraveneous, intramuscular, subcutaneous, intraarterial, intraperitoneal, intrathecal, etc.), for any disease (including both chronic and acute medical conditions, disorders, and the like). In addition, it is understood that the present invention is not limited to facilitating or improving the treatment of diseases. The present invention may be utilized to facilitate or improve the treatment of patients having various medical conditions, without limitation.

System Description

The present invention may be embodied as an expert system that provides decision support to physicians (or other health care providers) treating patients with a known disease, such as HIV infection. A system according to the present invention calculates combination antiretroviral therapy options and attaches all relevant information to those options.

As known to those of skill in the art, an expert system, also known as artificial intelligence (AI), is a computer program that can simulate the judgment and behavior of a human or an organization that has expert knowledge and experience in a particular field. An expert system typically contains a knowledge base containing accumulated experience and a set of rules for applying the knowledge base to each particular situation that is described to the program. Expert systems are well known to those of skill in the art and need not be described further herein.

The antiretroviral therapy options (combinations of antiretroviral drugs), are derived using a knowledge base consisting of a number of expert system rules and functions which in turn take into account a given patient's treatment history, current condition and laboratory values. A system according to the present invention supports the entry, storage, and analysis of patient data in a large central database. A system according to the present invention has a flexible data driven architecture and custom reporting capabilities designed to support patient therapy management and clinical drug trial activities such as screening, patient tracking and support. It is anticipated that a system according to the present invention may be used by health care providers (including physicians), clinical research scientists, and possibly healthcare organizations seeking to find the most cost-effective treatment options for patients while providing the highest standard of care.

A system **20** for carrying out the present invention is schematically illustrated in FIG. **2**. The system **20** comprises a knowledge base of treatment regimens **21**, which may be ranked for efficacy (e.g., by a panel of experts) or ranked according to system rules, a knowledge base of expert rules **22**, a knowledge base of advisory information **23**, a knowledge base of patient therapy history **24** and patient information **25**. Patient information is preferably stored within a database and is configured to be updated. The knowledge bases and patient information **21–25** may be updated by an input/output system **29**, which can comprise a keyboard (and/or mouse) and video monitor. Note also that, while the knowledge bases and patient data **21–25** are shown as separate blocks, the knowledge bases and patient data **21–25** can be combined together (e.g., the expert rules and the advisory information can be combined in a single database).

To carry out the method described above, the information from blocks **21–25** is provided to an inference engine **26**, which generates the listing of available treatments and the corresponding advisory information from the information provided by blocks **21–25**. The inference engine **26** may be implemented as hardware, software, or combinations thereof. Inference engines are known and any of a variety thereof may be used to carry out the present invention. Examples include, but are not limited to, those described in U.S. Pat. No. 5,263,127 to Barabash et al. (Method for fast rule execution of expert systems); U.S. Pat. No. 5,720,009 to Kirk et al. (Method of rule execution in an expert system using equivalence classes to group database objects); U.S. Pat. No. 5,642,471 to Paillet (Production rule filter mechanism and inference engine for expert system); U.S. Pat. No. 5,664,062 to Kim (High performance max-min circuit for a fuzzy inference engine).

High-speed inference engines are preferred so that the results of data entered are continually updated as new data is entered. As with the knowledge bases and patient information in blocks **21–25**, the inference engine **26** may be a separate block from the knowledge bases and patient information blocks **21–25**, or may be combined together in a common program or routine.

Note that the advisory information that is generated for any available therapy may differ from instance to instance based on differences in the patient information provided.

System Architecture

The present invention can be implemented as a system running on a stand alone computing device. Preferably, the present invention is implemented as a system in a client-server environment. As is known to those of skill in the art, a client application is the requesting program in a client-server relationship. A server application is a program that awaits and fulfills requests from client programs in the same or other computers. Client-server environments may include public networks, such as the Internet, and private networks often referred to as "intranets", local area networks (LANs) and wide area networks (WANs), virtual private networks

(VPNs), frame relay or direct telephone connections. It is understood that a client application or server application, including computers hosting client and server applications, or other apparatus configured to execute program code embodied within computer usable media, operates as means for performing the various functions and carries out the methods of the various operations of the present invention.

Referring now to FIG. **3**, a client-server environment **30** according to a preferred embodiment of the present invention is illustrated. The illustrated client-server environment **30** includes a central server **32** that is accessible by at least one local server **34** via a computer network **36**, such as the Internet. A variety of computer network transport protocols including, but not limited to TCP/IP, can be utilized for communicating between the central server **32** and the local servers **34**.

Central Server

The central server **32** includes a central database **38**, such as the Microsoft® SQL Server application program, version 6.5 (available from Microsoft, Inc., Redmond, WA), executing thereon. The central server **32** ensures that the local servers **34** are running the most recent version of a knowledge base. The central server **32** also stores all patient data and performs various administrative functions including adding and deleting local servers and users to the system (**20**, FIG. **2**). The central server **32** also provides authorization before a local server **34** can be utilized by a user. Patient data is preferably stored on the central server **32**, thereby providing a central repository of patient data. However, it is understood that patient data can be stored on a local server **34** or on local storage media.

Local Server

Each local server **34** typically serves multiple users in a geographical location. Each local server **34** includes a server application, an inference engine, one or more knowledge bases, and a local database **39**. Each local server **34** performs artificial intelligence processing for carrying out operations of the present invention. When a user logs on to a local server **34** via a client **35**, the user is preferably authenticated via an identification and password, as would be understood by those skilled in the art. Once authenticated, a user is permitted access to the system (**20**, FIG. **2**) and certain administrative privileges are assigned to the user.

Each local server **34** also communicates with the central server **32** to verify that the most up-to-date version of the knowledge base(s) and application are running on the requesting local server **34**. If not, the requesting local server **34** downloads from the central server **32** the latest validated knowledge base(s) and/or application before a user session is established. Once a user has logged onto the system (**20**, FIG. **2**) and has established a user session, all data and artificial intelligence processing is preferably performed on a local server **34**. An advantage of the illustrated client-server configuration is that most of the computationally intensive work occurs on a local server **34**, thereby allowing "thin" clients **35** (i.e., computing devices having minimal hardware) and optimizing system speed.

In a preferred embodiment, each local server database **39** is implemented via a Microsoft® SQL Server application program, Version 6.5. The primary purpose of each local database **39** is to store various patient identifiers and to ensure secure and authorized access to the system (**20**, FIG. **2**) by a user. It is to be understood, however, that both central and local databases **38**, **39** may be hosted on the central server **32**.

Local Client

Each local client **35** also includes a client application program that consists of a graphical user interface (GUI) and a middle layer program that communicates with a local server **34**. Program code for the client application program may execute entirely on a local client **35**, or it may execute partly on a local client **35** and partly on a local server **34**. As will be described below, a user interacts with the system (**20**, FIG. **2**) by entering (or accessing) patient data within a GUI displayed within the client **35**. The client **35** then communicates with a local server **34** for analysis of the displayed patient information.

Computer program code for carrying out operations of the present invention is preferably written in an object oriented programming language such as JAVA®, Smalltalk, or C++. However, the computer program code for carrying out operations of the present invention may also be written in conventional procedural programming languages, such as the "C" programming language, in an interpreted scripting language, such as Perl, or in a functional (or fourth generation) programming language such as Lisp, SML, or Forth.

The middle layer program of the client application includes an inference engine within a local server **34** that provides continuous on-line direction to users, and can instantly warn a user when a patient is assigned drugs or a medical condition that is contraindicated with, or antagonistic of, the patient's current antiretroviral therapy. Every time patient data is entered into the system (**20**, FIG. **2**) or updated, or even as time passes, the inference engine evaluates the current status of the patient data, sorting, categorizing, ranking and customizing every possible antiretroviral therapy for a patient according to the specific needs of the patient.

Inference Engine

Inference engines are well known by those of skill in the art and need not be described further herein. Each knowledge base used by an inference engine according to the present invention is a collection of rules and methods authored by a clinical advisory panel of HIV-treating physicians and scientists. A knowledge base may have subjective rules, objective rules, and system-generated rules. Objective rules are based on industry established facts regarding the treatment of HIV using antiretroviral therapy and are drawn from the package insert information of antiretroviral drug manufacturers and from peer reviewed and published journal articles. An example of an objective rule would be an antiretroviral to antiretroviral contraindication such as:

Rule #1: If the eval therapy contains Zidovudine (AZT) and Stavudine (d4T), then reject the therapy.

In Rule #1, the term "eval therapy" refers to the therapy currently being analyzed by the system (**20**, FIG. **2**). Rule #1 then states that if this therapy contains both AZT and d4T, then this therapy should not be displayed in a list of potential therapy options for the patient.

For objective rules, the present invention can be configured so as to prevent a user from receiving recommendations on new therapy options when certain crucial data on the patient has not been entered. However, it is understood that the present invention does not prevent a health care provider, such as a physician, from recording his/her therapy decisions, even if the system (**20**, FIG. **2**) has shown reasons why that therapy may be harmful to the patient. The present invention allows a health care provider to be the final authority regarding patient therapy.

Subjective rules are based on expert opinions, observations and experience. Subjective rules are typically developed from "best practices" information based on consensus opinion of experts in the field. Such expert opinion may be based on knowledge of the literature published or presented in the field or their own experience from clinical practice, research or clinical trials of approved and unapproved medications. A number of experts are used so that personal bias is reduced.

System generated rules are those derived from the outcomes of patients tracked in the system who received known and defined therapies and either improved, stabilized or worsened during a defined period. Because of the large number of potential combinations usable in HIV infection, this system generated database and rules derived from them are likely to encompass data beyond that achievable from objective or subjective rules databases.

The rules which comprise the various knowledge bases (**21–24**, FIG. **2**) of the present invention each have two main parts: a premise and a conclusion—also referred to as the left side and the right side, respectively. When a premise of a rule is found to be true, the action specified in the conclusion is taken. This is known to those of skill in the art as "firing" the rule. For example, consider the following rule:

Rule ID	Premise	Conclusion
FiltDComAl-If	the eval therapy contains ddC-	Commentary 18

The premise of the above rule is for the inference engine to determine whether or not a therapy being evaluated (i.e., "eval therapy") contains the antiretroviral drug "ddC". If a therapy does contain the antiretroviral drug ddC, the action called for by the conclusion of the rule is to attach "Commentary 18" to the therapy. Commentary 18 may be a piece of text that provides a user with the necessary information about therapies containing ddC.

Exemplary rules which may comprise one or more knowledge bases according to the present invention are listed below in Table 3.

TABLE 3

Therapy initiation/change: Rules that provide information on therapy change or initiation
Boundary condition rules: Limits for values, intervals for values to be updated
Comment Data Aging rules: These rules warn the user that the data in certain fields is getting old and that the most current values in the system will be used.
Rules that filter therapies due to drug interactions in ARV drug combinations
Rules that filter therapies due to medical conditions
Rules that filter therapies due to genotypic mutations in patient's plasma HIV
Rules that filter therapies due to phenotypic sensitivity/resistance
Antiretroviral therapy ranking rules
General dosage rules
Solid dosage rule
Dosage modifications due to ARV-ARV drug combination
Dosage modification due to ARV-NonARV interaction
Dosage modification due to medical condition
Comment determined
General commentary rules
Commentaries added due to medical conditions
Commentaries added due to drug interactions
Commentaries added due to drug combination
Delivery size rules

Using the various knowledge bases and patient information of the present invention (**21–25**, FIG. **2**), the inference engine (**26**, FIG. **2**) can evaluate potential therapy options for a patient based on a patient's medical history (including therapy history) and current laboratory values. Accordingly multiple antiretroviral drug combinations can be quickly and accurately analyzed for a particular patient. Furthermore, the inference engine can quickly provide guidance in the areas listed below in Table 4.

TABLE 4

Data Integrity	Is the patient lab and assessment data getting too old to be considered reliable? Are there conflicts between lab data such as phenotype data which indicates resistance to one or more antiretroviral drugs in the patient's current therapy and current viral load data which indicates significant viral suppression?
Therapy Performance	Should antiretroviral therapy be initiated for the patient? Is the patient's current therapy achieving good initial and long-term viral suppression or should the therapy be changed? Are there potential non-compliance issues as demonstrated by a lack of viral suppression with a regimen when current genotype or phenotype data does provide explanation for the failure by demonstrating resistance to any drugs in the patient current therapy?
Dosage	What are the base and adjusted dosages of antiretroviral drugs in a given therapy? Are there any special specific dosage administration instructions? What are options if patient can only take liquid dosage forms?
Contra-indications	Which antiretroviral drugs can be used with each other and what dosage adjustments are required? Are there any contraindications or interactions between antiretroviral drugs in patient's current therapy or potential therapies and the non-antiretroviral drugs patient is taking and if so what are they and what, if any, dosage adjustments are required?
Medical Conditions	Are there any medical conditions to be aware of in deciding an appropriate therapy for patient? What, if any, effect do current or historical medical conditions have on each therapy option?
Drug Cost and Delivery Data	How much does each therapy option cost? What is the dosing frequency of the drugs in the therapy? What is the pill count and optimum delivery size for the least number of pills?
Therapy Options	What are all the drug combination therapy options for patient? How can physician instantly assess which of the hundreds of potential combinations will be the most effective for patient? What information from the package inserts from each drug apply specifically to patient? What is the relative antiviral efficacy of each therapy? Are there special considerations that might make one therapy more or effective for patient?
Resistance	What drugs are patient's virus current genotypic or phenotypic profile known to be associated with resistance to? Which antiretroviral drugs are more effective against resistant strains when used together? Which drugs (if any) used in historical therapies are most likely to be effective if recycled into a new therapy? Can any of the drugs in patient's current therapy be recycled into the next therapy?

User Interface

Referring now to FIGS. **4–9**, exemplary user interfaces according to the present invention will be illustrated. In FIG. **4**, a medical history user interface **50** for entering data about a patient's medical history according to the present invention is illustrated. The medical history user interface **50** can be displayed by activating the "Medical History" tab **50***a*. The illustrated medical history user interface **50** allows a

user to create, save, update and print patient records. When a user adds a new patient, the medical history user interface **50** appears with empty data entry fields. Data entry fields for receiving information via a GUI are well known to those of skill in the art and need not be described further herein. When a user opens a patient record for editing, the medical history user interface **50** appears with patient data in the various fields. Preferably color is used to highlight critical or required information in a patient record.

Important elements in the illustrated medical history user interface **50** include a "print" button **51** for printing a patient record and therapeutic treatment regimen details; a "save" button **52** for saving a patient record; and a "speed entry" check box **53** for allowing a user to move quickly between entry fields. In addition, there are multiple group headings **54** that divide a patient's medical history into related categories. Each group contains entry fields in which a user can add patient information. An "add" button **55** allows a user to add new information to a patient record for a selected group. A "delete" button **56** allows a user to delete patient information for a selected group (although the original information is still recorded in the database). A "history" button **57** allows a user to review a patient's historical data for each selected group.

After completing a patient's medical history, an inference engine analyzes the data and suggests whether a therapeutic treatment regimen is indicated; if an existing therapeutic treatment regimen should be continued or changed; and the best drug therapies for the selected patient. Often, more than one drug therapy is presented to the user. These drug therapies are preferably ranked according to expected efficacy, frequency in dosage, pill count, and cost. All of these factors can help the user make a decision about what therapy to use for the selected patient. When a user clicks on a drug therapy in the presented list, information is provided about the dosage regimens. Also, various warnings, such as drug interaction warnings, and notes about each drug, are presented. An appropriate drug therapy can then be selected.

In FIG. **5**, an exemplary user interface chart **60** for monitoring a patient's condition during a particular drug therapy over a period of time is illustrated. The user interface chart **60** can be displayed by activating the "Chart" tab **60***a*. The illustrated user interface chart **60** tracks the CD4 level against viral load. Along the left-hand side of the Y-axis **61** the CD4 count is plotted. Along the right-hand side of the Y-axis **61** the viral load count is plotted. The lines **62** represent the CD4 test and the viral load test as would be understood by those having skill in the art. Drug therapy for a time period is indicated within the area of the chart user interface **60** indicated as **63**. Time is plotted along the X-axis **64**, as illustrated.

In FIG. **6**, a therapy evaluation user interface **70** that facilitates evaluation of various therapy options with respect to relative efficacy, dosage, frequency, cost, medical complications and drug interactions is illustrated. The therapy evaluation user interface **70** can be displayed by activating the "Therapy Evaluation" tab **70***a*. Important elements in the illustrated therapy evaluation user interface **70** include an "Evaluate Current Therapy" button **71** for initiating an evaluation of a current therapy and a "Current Therapy" field **72** that lists a patient's current therapy. Detailed information about a patient's therapy is displayed in the therapy details box **73**. A therapy displayed within box **73** is identified in box **74**.

Multiple check boxes **75** are provided that allow a user to control how information is displayed within the therapy evaluation user interface **70**. Within the therapy list box **76**, a list of available therapies for a patient can be displayed. In the illustrated embodiment the drugs are listed in standard abbreviated form. Other information displayed with each drug may include that listed below in Table 5.

TABLE 5

Efficacy Rating	Lists the therapy according to expected effectiveness only, regardless of patient specific considerations (1 is most effective).
Adjusted Score	This number uses the Efficacy Rating as a base and then the system adjusts it up or down based on patient specific conditions (1 is most effective).
Safety Considerations	A brief two or three word summary of the alerts associated with the therapy.
Frequency	Lists the dosage frequency (q12h, q24h, etc.).
Pills	Lists the total number of pills required per day for the complete regimen.
Cost	Lists the total cost of the regimen per day.
Medical Alert	Displays a Y if there is one or more Yellow Medical Alerts and an R ifthere is one or more Red Medical Alerts associated with the therapy.
Drug Interaction	Displays a Y if there is one or more Yellow Drug Interaction Alerts and an R if there is one or more Red Drug Interaction Alerts associated with the therapy.

A list of available antiretroviral drugs is displayed within box **77**. A user desiring to evaluate a particular combination of drugs can click the appropriate check boxes **77***a* to review information in the therapy details box **73**. A "Use as Current Therapy" button **78** allows a user to apply a particular therapy to a patient. Various hyperlinks **79** within the therapy details box **73** allow a user to display specific information about a therapy evaluation. For example, a user can be allowed to view a rule which is associated with the displayed text.

Resistance evaluation alerts **80** can be provided adjacent each available antiretroviral drug displayed within box **77**. For example, a blue "G" icon can be used to indicate that a patient's last genotype test contains mutations which are known to be associated with full or partial resistance to the antiretroviral drug. A red "P" icon can be used to indicate that a patient's last phenotype test demonstrates resistance to the antiretroviral drug.

Within the therapy list box **76**, various symbols (described in FIG. **7**) can be utilized to provide information about a drug therapy option. These symbols provide an instant graphical warning level for each therapy option. Some symbols, such as a red exclamation point, indicate that there is critical, possibly life threatening information in the therapy details box **73** for that therapy which must be read in order for that therapy to be properly utilized.

When a drug therapy from the therapy list box **76** is selected by a user for evaluation, the therapy details box **73** of FIG. **6** can be displayed in "full screen" mode as illustrated in FIG. **8**. Important elements in the illustrated therapy details box **73** include an identification box **73***a* for identifying the therapy being evaluated; a "Use as Current Therapy" button **78** that allows a user to apply a particular therapy to a patient; and a "Show Therapies" button **73***b* that returns the therapy details box **73** back to half-screen size as illustrated in FIG. **6**. In addition, various hyperlinks may be embedded within text displayed within the therapy details box **73** that can be activated by a user to display various types of information. Eye catching alert banner(s) **73***c* and text **73***d* can be displayed at the top of the therapy details box **73** as illustrated. Dosages **73***e* of each drug, along with

special administration instructions, can be displayed within the therapy details box **73** as illustrated. Dosage adjustment information **73***f* and various warnings and advisories **73***g* can also be displayed within the therapy details box **73** as illustrated.

According to a preferred embodiment of the present invention, therapeutic treatment regimens are not displayed to a user if an invalid drug is selected for treatment of a patient.

Physicians Desk Reference®

According to a preferred embodiment of the present invention, the Physicians Desk Reference® (PDR®) **28**, which is a known drug reference source, is fully integrated with the system **20** of FIG. **2**. Users can access the PDR® drug abstracts for antiretroviral drugs listed in the therapy list box **76** of the therapy evaluation user interface **70** of FIG. **6**. In addition, users can access the PDR® on-line Web database to obtain additional information about a specific drug or to research a substitute for a contraindicated drug. When a user selects a drug within the therapy list box **76** of the therapy evaluation user interface **70**, a web browser preferably is launched and the PDR® on-line Web database is accessed. Information can also be extracted from the PDR® on-line Web database to provide drug selection lists for non-antiretroviral drugs that a patient may be taking and to define relationships between brand name and generic drugs.

As illustrated in FIG. **9**, a PDR® pop-up menu **90** may be provided that can be activated from within the therapy list box **76** of the therapy evaluation user interface **70** of FIG. **6**. From the PDR® pop-up menu **90** a user can access various information from the PDR® including, but not limited to, drug abstracts, and generic components contained within a brand name drug.

The following non-limiting examples illustrate various aspects of the present invention. These examples are provided for illustrative purposes only, and are not intended to be limiting of the invention.

EXAMPLE 1

Example 1 will be explained with reference to FIGS. **10**A–**10**D. Referring to FIG. **10**A, a medical history user interface **50** containing evaluated data for patient "demo1" is illustrated. The group heading "Hemoglobin" **54***a* has changed colors to indicate to a user that the patient has an abnormally low hemoglobin value from a previous (historical) blood sampling. When the therapy evaluation tab **70***a* is activated to display the therapy evaluation user interface **70** (FIG. **10**B) the associated medical condition warning of a history of anemia and the caution notification if using drugs known to be associated with hematopoetic toxicity is triggered as illustrated in the therapy details box **73** of FIG. **10**B.

In addition, the group heading "Renal Function" **54***b* in FIG. **10**A has changed colors to warn a user of potential renal dysfunction and is also indicated by the low estimated creatinine clearance rate in field F**1** (which the system calculates using a mathematical formula taking patient age, sex, weight, and serum creatinine values—all of which are fields of the "Medical History" user interface **50**). This information is pointed out to the user and is used if dosage adjustments are required for drugs that are known to be affected (cleared) by renal function.

Current and the next most recent $CD4^+$ cell count and viral load are displayed (F**2**, medical history user interface **50**). This information is also used to determine when to start or change therapy and to evaluate the initial antiviral efficacy of a newly administered antiviral regimen.

Current and historical values for all fields in the medical history user interface **50** (FIG. **10**A) can be viewed by pressing the "H" button beside fields that have this button.

In FIG. **10**C, the "Chart" user interface **60** has been activated. HIV RNA (viral load) is plotted on a log scale, the CD4 count is plotted on a linear scale, and the drug treatments are shown as Gantt bars on the horizontal date scale at the bottom of the chart user interface **60**.

In FIG. **10**D, the "Change Therapy Recommendation" message box MB**1** pops up when the "Therapy Evaluation" tab **70***a* is selected. This box represents the processing of the data from the "Medical History" tab and the knowledge base output, including objective rules derived from published treatment guidelines, indicating that initiation of therapy, or a change of therapy in this case, may be called for if the other variable(s) indicated in the message have been addressed.

The list of available therapies and associated ranking order may be shown within the therapy details box **73** of FIG. **10**B. This represents the output of the knowledge base for therapy selection. Included with the list of therapies can be any of the following: safety advisories (dosage adjustment, drug interaction, etc.) with a yellow triangle or red exclamation warning symbols; number of pills; daily cost of all three drugs; dosing regimen (q 8 h, q 12 h, etc.); and dosages for all drugs in a regimen (including dosage adjustments if necessary) and pertinent information specific to the patient is listed in the dialog box.

EXAMPLE 2

Example 2 will be explained with reference to FIGS. **11**A–**11**E, and relates to patient file "ARV naive**1**" which is an example of an HIV-infected patient who has not been treated with anti-HIV drugs previously. In FIG. **11**A, a medical history user interface **50** containing evaluated data for patient "ARV naive**1**" is illustrated. In FIG. **11**B, when the "Therapy Evaluation" tab **70***a* is activated to display the therapy evaluation user interface **70**, a "Boundary and Prequalification Messages" message box MB**2** pops up indicating that according to the current, published, HIV treatment guidelines, the patient should be initiated on antiviral therapy and that the current guidelines recommend combinational therapy.

In FIG. **11**C, the therapy evaluation user interface **70** has been activated and demonstrates features/functions associated with therapy evaluation including a general warning **W1** and advisories **A1**, **A2**, and **A3** for the patient related to treatment of the disease (e.g., whether therapy should be initiated or changed) or related to a specific therapy selected from the list box which is being evaluated by the user.

FIG. **11**D illustrates various information that is displayable by clicking on an individual therapy in the therapy list box **76** of FIG. **11**C. Information displayed includes dosages of all drugs with general and patient-specific warnings and advisories.

The features available by right clicking on any therapy listed in the therapy list box **76** of FIG. **11**C are illustrated in FIG. **11**E and include: linking to an electronic PDR® to show drug package insert information or perform drug search information; showing or hiding columns of information displayed within the therapy list box; linking to a publication or abstract associated with a therapy that has a "book" icon associated therewith; and various printing functions.

EXAMPLE 3

Example 3 will be explained with reference to FIGS. **12A–12C**, and relates to patient file "Featuresl" which illustrates some important functions/features that a system according to the present invention can provide for highly drug experienced patients who may have developed resistance associated with the use of several antiviral drugs. Features, including functions attributed to the new resistance and historical therapy rules are illustrated and includes:

1) Potential drug resistance advisories (**A1**, FIG. **12A**) when the chart tab **60***a* is activated, or (**A2**, FIG. **12B**) when the therapy evaluation tab **70***a* is activated;

2) The heads up "P" and "G" indicators (**I1** and **I2**, FIG. **12B**) to remind of phenotypic or genotypic resistance associated with certain anti-HIV compounds as demonstrated for this patient (including indication of expected/anticipated genotypic resistance, as a result of cross-resistance, to a drug that a patient may not be taking currently or has not previously taken);

3) The drug interaction warning system (indicated by warning **W3**, FIG. **12C**). Warning **W3** is for the interaction between Nevirapine and rifabutin (which was selected from the list of non-antiretroviral drugs available as part of the medical history user interface **50**). The drug interaction warning message may be viewed from the medical history user interface **50** by "right-clicking" the non-ARV title bar **54**C, which has turned yellow indicating the presence of an ARV-nonARV drug interaction. This information is also prominently displayed for the user on the therapy evaluation user interface **70** as a text message (**W3**, FIG. **12B**) as well as in the "Safety Considerations" section of the drug list box (**76**, FIG. **12B**); and

4) The chart user interface **60** (FIG. **12A**) illustrates the viral load, CD4, drug therapies, and associated drug resistance in graphic form for the user to evaluate.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That which is claimed is:

1. A method for guiding the selection of a therapeutic treatment regimen for a patient with a chronic known disease or medical condition, said method comprising:

(a) providing patient information to a computing device, said patient information including prior therapeutic treatment regimen information for said chronic known disease or medical condition, said computer device comprising:

a first knowledge base comprising a plurality of different therapeutic treatment regimens for said disease or medical condition;

a second knowledge base comprising a plurality of expert rules for evaluating and selecting a therapeutic treatment regimen for said disease or medical condition;

a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of said different therapeutic treatment regimens; and

(b) generating in said computing device from said patient information and said first knowledge base a listing of available therapeutic treatment regimens for said patient; and

(c) generating in said computing device advisory information for one or more therapeutic treatment regimens for said patient in said listing based on said patient information and said expert rules.

2. A method according to claim **1**, further comprising the steps of:

(d) entering a user-defined therapeutic treatment regimen for said disease or medical condition that is not included in said first knowledge base;

(e) generating in said computing device advisory information for said user-defined combination therapeutic treatment regimen.

3. A method according to claim **1**, further comprising the steps of:

(f) entering a non-recommended therapeutic treatment regimen for said disease or medical condition that is included in said first knowledge base but not recommended from said listing; and

(g) generating in said computing device advisory information for said non-recommended therapeutic treatment regimen, said advisory information including at least one reason for non-recommendation of said therapeutic treatment regimen.

4. A method according to claim **1**, said patient information comprising gender, age, weight, CD4 information, viral load information, HIV genotype and phenotype information, hemoglobin information, neuropathy information, neutrophil information, pancreatitis, hepatic function, renal function, drug allergy and intolerance information.

5. A method according to claim **1**, wherein said listing of available therapeutic treatment regimens for said patient comprises a ranked listing of available therapeutic treatment regimens for said patient.

6. A method according to claim **1**, wherein said patient information includes prior patient information stored in said computing device.

7. A method according to claim **1**, said advisory information including:

warnings to take the patient off a contraindicated drug before initiating a corresponding therapeutic treatment regimen; and

information clinically useful to implement a corresponding therapeutic treatment regimen.

8. A method according to claim **1**, wherein said computing device comprises a fourth knowledge base comprising patient therapeutic treatment regimen history, said advisory information including previous therapeutic treatment regimen information extracted from said fourth knowledge base.

9. A method according to claim **7**, wherein said known disease or medical condition is HIV-1 infection, said therapeutic treatment regimen includes antiretroviral drugs, and said therapeutic treatment regimen includes contraindicated or potentially adversely interacting non-antiretroviral drugs.

10. A method according to claims **7**, wherein said therapeutic treatment regimen includes a protease inhibitor, and said contraindicated drug is terfenadine.

11. A method according to claim **7**, wherein said therapeutic treatment regimen includes indinavir and said contraindicated drug is cisapride.

12. A method according to claim 1, wherein said known disease or medical condition is one where multiple prophylactic or therapeutic treatment regimens are available to be used singly or in combination in the treatment of said disease.

13. A method according to claim 1, wherein said known disease or medical condition is a cardiovascular disease.

14. A method according to claim 1, wherein said known disease or medical condition is a pulmonary disease.

15. A method according to claim 1, wherein said known disease or medical condition is a neurologic disease.

16. A method according to claim 1, wherein said known disease or medical condition is cancer.

17. A method according to claim 1, wherein said known disease or medical condition is a urinary tract infection.

18. A method according to claim 1, wherein said known disease or medical condition is hepatitis.

19. A method according to claim 1, wherein said known disease or medical condition is HIV-1 infection.

20. A method according to claim 1, wherein said first knowledge base comprises a plurality of different combination therapeutic treatment regimens.

21. A method according to claim 1, wherein drug dosage information is recommended and adjusted if necessary depending upon said patient information.

22. A method according to claim 1, further comprising the step of:

(d) accessing, via said computing device, information for one or more therapeutic treatment regimens from a drug reference source.

23. A system for guiding the selection of a therapeutic treatment regimen for a patient with a chronic known disease or medical condition, said system comprising:

(a) a computing device comprising:

a first knowledge base comprising a plurality of different therapeutic treatment regimens for said disease or medical condition;

a second knowledge base comprising a plurality of expert rules for selecting a therapeutic treatment regimen for said disease or medical condition;

a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of said different therapeutic treatment regimens; and

(b) means for providing patient information to said computing device, said patient information including prior therapeutic treatment regimen information for said chronic known disease or medical condition;

(c) means for generating in said computing device from said patient information and said first knowledge base a listing of therapeutic treatment regimens for said patient for said chronic known disease or medical condition; and

(d) means for generating in said computing device advisory information for one or more therapeutic treatment regimens for said patient in said listing based on said patient information and said expert rules.

24. A system according to claim 23, further comprising:

(e) means for entering a user-defined therapeutic treatment regimen for said disease or medical condition that is not generated or displayed via said first knowledge base;

(f) means for generating in said computing device advisory information for said user-defined combination therapeutic treatment regimen.

25. A system according to claim 23, further comprising:

(f) means for entering a non-recommended therapeutic treatment regimen for said disease or medical condition that is included in said first knowledge base but not recommended from said listing; and

(g) means for generating in said computing device advisory information for said non-recommended therapeutic treatment regimen, said advisory information including at least one reason for non-recommendation of said therapeutic treatment regimen.

26. A system according to claim 23, said patient information comprising gender, age, weight, CD4 information, viral load information, HIV genotype and phenotype information, hemoglobin information, neuropathy information, neutrophil information, pancreatitis, hepatic function, renal function, drug allergy and intolerance information.

27. A system according to claim 23, wherein said listing of available therapeutic treatment regimens for said patient comprises a ranked listing of available therapeutic treatment regimens for said patient.

28. A system according to claim 23, wherein said patient information includes prior patient information stored in said computing device.

29. A system according to claim 23, said advisory information including:

warnings to take the patient off a contraindicated drug before initiating a corresponding therapeutic treatment regimen; and

information clinically useful to implement a corresponding therapeutic treatment regimen.

30. A system according to claim 23, wherein said computing device comprises a fourth knowledge base comprising patient therapeutic treatment regimen history, said advisory information including previous therapeutic treatment regimen information extracted from said fourth knowledge base.

31. A system according to claim 29, wherein said known disease or medical condition is HIV-1 infection, said therapeutic treatment regimen includes antiretroviral drugs, and said therapeutic treatment regimen includes contraindicated or potentially adversely interacting non-antiretroviral drugs.

32. A system according to claim 29, wherein said therapeutic treatment regimen includes a protease inhibitor, and said contraindicated drug is terfenadine.

33. A system according to claim 29, wherein said therapeutic treatment regimen includes indinavir and said contraindicated drug is cisapride.

34. A system according to claim 23, wherein said known disease or medical condition is one where multiple prophylactic therapeutic treatment regimens are available to be used singly or in combination in the treatment of said disease or medical condition.

35. A system according to claim 23, wherein said known disease or medical condition is a cardiovascular disease.

36. A system according to claim 23, wherein said known disease or medical condition is a pulmonary disease.

37. A system according to claim 23, wherein said known disease or medical condition is a neurologic disease.

38. A system according to claim 23, wherein said known disease or medical condition is cancer.

39. A system according to claim 23, wherein said known disease or medical condition is a urinary tract infection.

40. A system according to claim 23, wherein said known disease or medical condition is hepatitis.

41. A system according to claim 23, wherein said known disease or medical condition is HIV-1 infection.

42. A system according to claim 23, wherein said first knowledge base comprises a plurality of different combination therapeutic treatment regimens.

43. A system according to claim 23, wherein drug dosage information is recommended and adjusted if necessary depending upon said patient information.

44. A system according to claim further comprising:

(e) means for accessing, via said computing device, information for one or more therapeutic treatment regimens from a standard drug reference source.

45. A computer program product for guiding the selection of a therapeutic treatment regimen for a patient with a chronic known disease or medical condition, said computer program product comprising a computer usable storage medium having computer readable program code means embodied in the medium, the computer readable program code means comprising:

(a) computer readable program code means for generating:

a first knowledge base comprising a plurality of different therapeutic treatment regimens for said disease or medical condition;

a second knowledge base comprising a plurality of expert rules for selecting a therapeutic treatment regimen for said disease or medical condition;

a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of said different therapeutic treatment regimens; and

(b) computer readable program code means for providing patient information, said patient information including prior therapeutic treatment regimen information for said chronic known disease or medical condition;

(c) computer readable program code means for generating from said patient information and said first knowledge base a listing of available therapeutic treatment regimens for said patient for said chronic known disease or medical condition; and

(d) computer readable program code means for generating advisory information for one or more therapeutic treatment regimens for said patient in said listing based on said patient information and said expert rules.

46. A computer program product according to claim 45, further comprising:

(e) computer readable program code means for entering a user-defined therapeutic treatment regimen for said disease or medical condition that is not generated or displayed via said first knowledge base;

(f) computer readable program code means for generating advisory information for said user-defined combination therapeutic treatment regimen.

47. A computer program product according to claim 46, further comprising:

(g) computer readable program code means for entering a non-recommended therapeutic treatment regimen for said disease or medical condition that is included in said first knowledge base but not recommnended from said listing; and

(h) computer readable program code means for generating advisory information for said non-recommended therapeutic treatment regimen, said advisory information including at least one reason for non-recommendation of said therapeutic treatment regimen.

48. A computer program product according to claim 45, said patient information comprising gender, age, weight, CD4 information, viral load information, HIV genotype and phenotype information, hemoglobin information, neuropathy information, neutrophil information, pancreatitis, hepatic function, renal function, drug allergy and intolerance information.

49. A computer program product according to claim 45, wherein said patient information includes prior patient information.

50. A computer program product according to claim 45, said advisory information including:

warnings to take the patient off a contraindicated drug before initiating a corresponding therapeutic treatment regimen; and

information clinically useful to implement a corresponding therapeutic treatment regimen.

51. A computer program product according to claim 45 wherein said computer readable program code means comprises computer readable program code means for generating a fourth knowledge base comprising patient therapeutic treatment regimen history, said advisory information including previous therapeutic treatment regimen information extracted from said fourth knowledge base.

52. A computer program product according to claim 50, wherein said known disease or medical condition is HIV-1 infection, said therapeutic treatment regimen includes antiretroviral drugs, and said therapeutic treatment regimen includes contraindicated or potentially adversely interacting non-antiretroviral drugs.

53. A computer program product according to claim 50, wherein said therapeutic treatment regimen includes a protease inhibitor, and said contraindicated drug is terfenadine.

54. A computer program product according to claim 50, wherein said therapeutic treatment regimen includes indinavir and said contraindicated drug is cisapride.

55. A computer program product according to claim 45, wherein said known disease or medical condition is one where multiple prophylactic therapeutic treatment regimens are available to be used singly or in combination in the treatment of said disease or medical condition.

56. A computer program product according to claim 45, wherein said known disease or medical condition is a cardiovascular disease.

57. A computer program product according to claim 45, wherein said known disease or medical condition is a pulmonary disease.

58. A computer program product according to claim 45, wherein said known disease or medical condition is a neurologic disease.

59. A computer program product according to claim 45, wherein said known disease or medical condition is cancer.

60. A computer program product according to claim 45, wherein said known disease or medical condition is a urinary tract infection.

61. A computer program product according to claim 45, wherein said known disease or medical condition is hepatitis.

62. A computer program product according to claim 45, wherein said known disease or medical condition is HIV-1 infection.

63. A computer program product according to claim 45, wherein said first knowledge base comprises a plurality of different combination therapeutic treatment regimens.

64. A computer program product according to claim 45, wherein drug dosage information is recommended and adjusted if necessary depending upon said patient information.

65. A computer program product according to claim 45, further comprising:

(e) computer readable program code means for accessing information for one or more therapeutic treatment regimens from a standard drug reference source.

66. A computer program product according to claim 45, wherein said listing of available therapeutic treatment regimens for said patient is a ranked listing of available therapeutic treatment regimens for said patient.

* * * * *

US006188988C1

(12) EX PARTE REEXAMINATION CERTIFICATE (7412th)

United States Patent

Barry et al.

(10) Number: US 6,188,988 C1

(45) Certificate Issued: *Mar. 23, 2010

(54) **SYSTEMS, METHODS AND COMPUTER AND COMPUTER PROGRAM PRODUCTS FOR GUIDING THE SELECTION OF THERAPEUTIC TREATMENT REGIMENS**

(75) Inventors: **David W. Barry**, Chapel Hill, NC (US); **Carolyn S. Underwood**, Cary, NC (US); **Bruce J. McCreedy**, Raleigh, NC (US); **David D. Hadden**, Durham, NC (US); **Jason L. Lucas**, West Chester, PA (US)

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Reexamination Request:
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(*) Notice: This patent is subject to a terminal disclaimer.

Related U.S. Application Data

(63) Continuation of application No. 09/283,702, filed on Apr. 1, 1999, now Pat. No. 6,081,786.

(60) Provisional application No. 60/080,629, filed on Apr. 3, 1998.

(51) **Int. Cl.**
G06F 19/00 (2006.01)

(52) **U.S. Cl.** **705/3**; 705/2; 706/45; 706/46; 706/47; 706/924

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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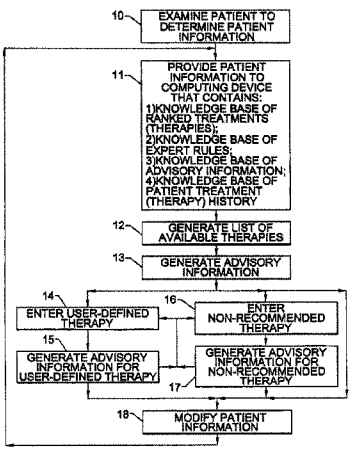
Primary Examiner—Deandra M. Hughes

(57) **ABSTRACT**

Systems, methods and computer program products for guiding selection of a therapeutic treatment regimen for a known disease such as HIV infection are disclosed. The method comprises (a) providing patient information to a computing device (the computer device comprising: a first knowledge base comprising a plurality of different therapeutic treatment regimens for the disease; a second knowledge base comprising a plurality of expert rules for selecting a therapeutic treatment regimen for the disease; and a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of the different therapeutic treatment regimens; and (b) generating in the computing device a listing (preferably a ranked listing) of therapeutic treatment regimens for the patient; and (c) generating in the computing device advisory information for one or more treatment regimens in the listing based on the patient information and the expert rules.

At the time of issuance and publication of this certificate, the patent remains subject to pending reexamination control numbers 95/001,088 and 90/009,213 filed Oct. 10, 2008 and Oct. 14, 2008 respectively. The claim content of the patent may be subsequently revised. Patent is issued from the reissue application.



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EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1**–**66** is confirmed.

* * * * *

US006188988C2

(12) **INTER PARTES REEXAMINATION CERTIFICATE** (0207th)

United States Patent

Barry et al.

(10) **Number: US 6,188,988 C2**

(45) **Certificate Issued: *Nov. 9, 2010**

(54) **SYSTEMS, METHODS AND COMPUTER PROGRAM PRODUCTS FOR GUIDING THE SELECTION OF THERAPEUTIC TREATMENT REGIMENS**

(75) Inventors: **David W. Barry**, Chapel Hill, NC (US); **Carolyn S. Underwood**, Cary, NC (US); **Bruce J. McCreedy**, Raleigh, NC (US); **David D. Hadden**, Durham, NC (US); **Jason L. Lucas**, West Chester, PA (US)

(73) Assignee: **Advanced Biological Laboratories, SA**, Luxembourg (LU)

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(51) **Int. Cl.**
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(52) **U.S. Cl.** **705/3**; 705/2; 706/45; 706/46; 706/47; 706/924

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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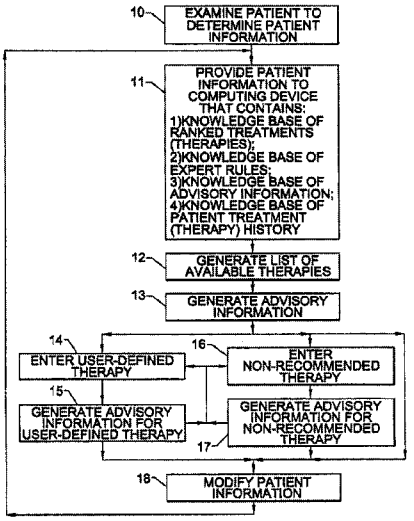
Primary Examiner—Deandra M Hughes

(57) **ABSTRACT**

Systems, methods and computer program products for guiding selection of a therapeutic treatment regimen for a known disease such as HIV infection are disclosed. The method comprises (a) providing patient information to a computing device (the computer device comprising: a first knowledge base comprising a plurality of different therapeutic treatment regimens for the disease; a second knowledge base comprising a plurality of expert rules for selecting a therapeutic treatment regimen for the disease; and a third knowledge base comprising advisory information useful for the treatment of a patient with different constituents of the different therapeutic treatment regimens; and (b) generating in the computing device a listing (preferably a ranked listing) of therapeutic treatment regimens for the patient; and (c) generating in the computing device advisory information for one or more treatment regimens in the listing based on the patient information and the expert rules.



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INTER PARTES REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 316

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **1-66** is confirmed.

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