

Table S1. Types of non–liver-related non–AIDS-related events**Cardiovascular events**

- Coronary
 - Acute myocardial infarction
 - Angina
 - Sudden death from possible coronary etiology
- Cerebrovascular
 - Transient ischemic attack
 - Reversible ischemic deficit
 - Established stroke
 - Asymptomatic cerebrovascular disease
- Peripheral arterial disease
- Congestive heart failure
- Primary pulmonary hypertension

Renal events

- Chronic renal failure
- Initiation of dialysis
- Kidney transplantation

Bone-related events

- Vertebral fracture
- Large bone fracture
- Osteonecrosis (avascular necrosis of bone)

Metabolic events

- Diabetes mellitus

Cancer (non–liver-related non–AIDS-related)

- Anus
- Brain
- Breast
- Colorectal
- Esophagus
- Head and neck
- Hodgkin lymphoma
- Kidney
- Lung
- Melanoma
- Non-melanoma skin
- Other hematologic non–AIDS-related
- Penis
- Prostate
- Sarcoma
- Stomach
- Testicle
- Vagina/vulva
- Other

Non–AIDS-related infections

- Sepsis requiring hospitalization

Table S2. Definitions of non–liver-related non–AIDS-related events**1) Cardiovascular Events****A) Coronary****Acute myocardial infarction:**

Acute myocardial infarction is defined as the presence of any of the following criteria:

1. ECG diagnosis or
2. Symptoms + probable ECG + elevated levels of cardiac biomarkers
3. Typical symptoms + elevated levels of cardiac biomarkers + ECG with signs of ischemia, or ECG not classifiable or not available.
4. Fatal cases with the macroscopic appearance of recent myocardial infarction and/or recent coronary occlusion in autopsy

ECG changes:

- Diagnostic ECG: (a) appearance of unambiguous Q waves; if the Q wave is ambiguous, it must be accompanied by alterations in the ST segment or T wave; all these changes must be accompanied by a progression in the T wave in 3 or more leads; (b) ST-segment elevation that lasts more than 24 hours with T-wave progression in 3 or more leads.
- Probable ECG: (a) Non-significant drop in the T segment in a recording accompanied by significant drop in another recording; or (b) Non-significant ST elevation in a recording accompanied by significant elevation in another recording; or (c) Non-significant T wave reversal in a recording accompanied by significant reversal in another recording.
- ECG with signs of ischemia: corresponds to ECG abnormalities that have not progressed.
- ECG not coded: for technical reasons or intrinsic conduction disturbances/arrhythmias.

Elevation of cardiac enzymes:

Including creatine kinase (CK) (and the MB isoenzyme of CK), LDH, cardiac-specific troponin T and cardiac-specific troponin I. Documented elevations of aminotransferases are also accepted.

Symptoms:

Typical:

- Crushing chest pain or angina pectoris (any synonym for pain is acceptable e.g., "pressure", "discomfort")
- Duration of more than 20 minutes
- Absence of non-atherosclerotic cardiac or non-cardiac causes.

Atypical:

- Atypical pain (short duration or intermittent), episode lasting less than 20 minutes, or at an unusual location (upper abdomen, arms, jaw, neck).
- Acute left ventricular failure
- Shock
- Syncope
- No underlying disease other than ischemic heart disease
- No definitive non-atherosclerotic cardiac or non-cardiac cause

Angina

Symptoms suggestive of myocardial ischemia, such as chest tightness and pain or pain in the jaw or arm. The pain usually lasts less than 20 minutes. ECG changes (e.g., depression of at least 0.5 mm of the ST segment or T-wave inversion of at least 1 mm in 2 or more contiguous leads) must objectively confirm myocardial ischemia.

Stable angina:

- Angina that has not changed its frequency or characteristics during the last 6 weeks. It is controlled with rest or treatment.

Unstable angina:

- Angina during inactivity, usually lasting more than 20 minutes.
- Angina of recent onset.
- Recent progression of angina reflected by an increase in severity.

B) Cerebrovascular

The diagnosis of cerebral hemorrhage is established with CT or MRI; ischemic episodes are confirmed based on clinical and radiological data: onset of neurological deficit in which other causes (space-occupying lesions in the brain, meningoencephalitis) are ruled out and monitoring during the following hours confirmed signs of cerebral ischemia in the imaging tests.

Transient ischemic attack

Episode of focal neurologic dysfunction caused by ischemia of a brain area that lasts less than 24 hours.

Reversible ischemic deficit

Episode of focal neurologic dysfunction of more than 24 hours' duration with subsequent recovery.

Established stroke

Neurological deficit that does not change during the first 24-72 hours of observation.

Asymptomatic cerebrovascular disease

Neuroimaging studies showing ischemic brain lesions that have not produced clinical manifestations (silent infarcts) in patients with risk factors.

C) Peripheral arterial disease

Peripheral arterial disease is defined as the presence of atherosclerosis in the arteries of the lower extremities. It is characterized by intermittent claudication or other clinical manifestations that indicate a more advanced stage, such as ischemic pain at rest, blue toe syndrome, non-healing ulcers or focal gangrene, with objective evidence of peripheral arterial disease, i.e., an ankle-brachial index (ABI) at rest of <0.9 . In addition to ABI, the test results considered accepted as objective evidence of peripheral arterial disease included the following: Doppler ultrasound, MRI angiography, and CT angiography. Also included in this group are patients undergoing arterial revascularization or amputation.

D) Heart failure

Heart failure is defined as compatible symptoms that correspond to functional classes II to IV of the New York Heart Association (NYHA): class II (mild), slight limitation to ordinary physical activities, such as those arising from palpitations or dyspnea, without dyspnea at rest; class III (moderate), marked limitation to ordinary physical activities without dyspnea at rest; class IV (severe), inability to perform any physical activity, dyspnea at rest.

The aforementioned symptoms are accompanied by a ventricular ejection fraction ≤ 0.40 on echocardiography (Hjalmarson A, JAMA 2000; 283: 1295-302).

E) Pulmonary hypertension

Pulmonary arterial hypertension was defined as a mean pulmonary artery pressure of ≥ 25 mmHg and a pulmonary capillary wedge pressure of ≤ 15 mmHg at rest (Galiè N, N Engl J Med 2005; 353: 2148-57).

2) Renal events

A) Chronic renal failure

Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for more than 3 months. eGFR can be calculated using the CKD-EPI or MDRD formulas.

B) Initiation of hemodialysis or peritoneal dialysis

C) Kidney transplantation

3) Bone events

A) Osteonecrosis (avascular necrosis of bone)

A diagnosis of osteonecrosis is confirmed when definite or probable criteria are met

Definite osteonecrosis

- Histological confirmation
- When 2 of the following criteria are met:
 - 1) Compatible findings in a plain radiograph: i) line of subchondral fracture or depression of the femoral head and/or ii) band sclerosis of the femoral head.
 - 2) Compatible bone scan findings: area of low uptake surrounded by an area of high uptake (known as the “cold in hot” pattern).
 - 3) Typical MRI findings: a high-intensity region of bone marrow edema accompanied by a peripheral band of low signal intensity on both T1- and T2-weighted images separating the osteonecrosis from the surrounding healthy bone marrow.

Probable osteonecrosis

Clinical and radiological suspicion, but 2 of the above criteria are not met

B) Spinal fracture

The diagnosis is clinical and radiological. The presence of fracture is defined as a visual estimation of a reduction in the vertebral height (anterior, middle, or posterior) $\geq 20\%$ in a plain radiograph of the spine in lateral projection (Genant HKJ Bone Miner Res 1993).

C) Long-bone fracture

The diagnosis is clinical and radiological. Long-bone fracture is defined as a break in the continuity of bone with or without separation of the fragments on a plain radiograph.

4) Metabolic events

A) Diabetes mellitus

- Fasting plasma glucose (FPG) >126 mg/dL (7.0 mmol/L) on at least 2 separate consecutive occasions, no evidence of glucose levels in the normal range.
- In the absence of information on FPG levels, diagnosis can be established in either of the following circumstances:
 - Symptoms of diabetes + blood glucose concentration >200 mg/dL (11.1 mmol/L), or
 - Plasma glucose 2 hours after a glucose tolerance test >200 mg/dL (11.1 mmol/L), or
 - The diagnosis was made elsewhere, and the patient was started on antidiabetic therapy

5) Cancer (non-AIDS-related non-liver-related)

The diagnosis requires histopathological confirmation.

6) Non-AIDS-related infections

A) Sepsis requiring hospitalization

Sepsis is defined as systemic inflammatory response syndrome (SIRS) caused by an infectious process at any location

- SIRS is defined by the presence of at least 2 of the following criteria
 1. Fever ($>38^{\circ}\text{C}$) or hypothermia ($<36^{\circ}\text{C}$)
 2. Increased heart rate ($>90/\text{min}$)
 3. Tachypnea ($>20/\text{min}$) or hyperventilation ($\text{PaCO}_2 <32$ mmHg)
 4. $\text{WBC} >12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$ or the presence of $>10\%$ neutrophils.
- Infection can be established based on the presence of positive blood cultures or a compatible clinical picture without positive blood cultures.

Table S3. Exposure to antiretroviral drugs that have been associated with chronic renal failure or cardiovascular disease during the study period

Antiretroviral drug	No SVR (n=997)	SVR (n=628)	Total (N=1625)	P
Tenofovir disoproxil fumarate				
Ever exposed, No. (%)	609 (61.1)	376 (59.9)	985 (60.6)	.627
Cumulative exposure, years, median (IQR)	3.32 (1.84 - 4.80)	3.46 (2.01 - 5.05)	3.42 (1.91 - 4.92)	.192
Didanosine				
Ever exposed, No. (%)	186 (18.7)	78 (12.4)	264 (16.2)	.001
Cumulative exposure, years, median (IQR)	2.85 (1.56 - 4.77)	3.52 (1.98 - 5.69)	3.15 (1.72 - 4.96)	.036
Abacavir				
Ever exposed, No. (%)	269 (27.0)	141 (22.5)	410 (25.2)	.041
Cumulative exposure, years, median (IQR)	3.23 (1.68 - 4.83)	3.93 (2.49 - 5.42)	3.62 (1.89 - 5.00)	.002
Indinavir				
Ever exposed, No. (%)	24 (2.4)	19 (3.0)	43 (2.6)	.450
Cumulative exposure, years, median (IQR)	2.16 (1.78 - 2.63)	2.78 (2.17 - 4.32)	2.34 (1.85 - 3.19)	.035
Lopinavir				
Ever exposed, No. (%)	279 (28.0)	137 (21.8)	416 (25.6)	.006
Cumulative exposure, years, median (IQR)	2.97 (1.46 - 4.81)	3.61 (2.01 - 5.18)	3.22 (1.72 - 4.9)	.038

Table S4. Sensitivity analysis with patients classified according to reinfections and retreatments

Adjusted hazards for events during follow-up for 997 non-responders to interferon plus ribavirin compared with 628 responders according to the type of analysis ^{a,b}

	Primary analysis		Second analysis		Third analysis		Fourth analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Overall deaths	0.36 (0.24 - 0.54)	<.001	0.35 (0.23 - 0.53)	<.001	0.32 (0.21 - 0.49)	<.001	0.35 (0.23 - 0.52)	<.001
	sHR (95% CI)	<i>P</i>	sHR (95% CI)	<i>P</i>	sHR (95% CI)	<i>P</i>	sHR (95% CI)	<i>P</i>
Cause-specific deaths								
LR	0.13 (0.06 - 0.28)	<.001	0.13 (0.06 - 0.29)	<.001	0.12 (0.05 - 0.27)	<.001	0.12 (0.05 - 0.27)	<.001
NLR	0.73 (0.44 - 1.20)	.214	0.70 (0.42 - 1.18)	.180	0.65 (0.38 - 1.12)	.117	0.70 (0.42 - 1.15)	.161
AR	0.37 (0.09 - 1.43)	.148	0.37 (0.10 - 1.46)	.155	0.39 (0.11 - 1.42)	.153	0.36 (0.09 - 1.41)	.144
NLR NAR	0.79 (0.47 - 1.35)	.388	0.76 (0.44 - 1.32)	.330	0.69 (0.39 - 1.25)	.223	0.76 (0.45 - 1.29)	.305
New AR events	0.37 (0.17 - 0.79)	.010	0.38 (0.17 - 0.85)	.019	0.25 (0.1 - 0.64)	.004	0.34 (0.16 - 0.72)	.005
LR events								
Decompensation	0.10 (0.05 - 0.21)	<.001	0.06 (0.02 - 0.15)	<.001	0.06 (0.02 - 0.17)	<.001	0.07 (0.03 - 0.17)	<.001
HCC	0.13 (0.03 - 0.50)	.003	0.06 (0.01 - 0.43)	.005	0.09 (0.01 - 0.65)	.017	0.06 (0.01 - 0.42)	.005
Transplantation	0.12 (0.02 - 0.78)	.027	NA	NA	NA	NA	NA	NA
NLR NAR events								
Diabetes mellitus *	0.57 (0.35 - 0.93)	.024	0.49 (0.29 - 0.83)	.007	0.52 (0.30 - 0.91)	.021	0.48 (0.29 - 0.80)	.005
NLR-NAR cancer	0.91 (0.58 - 1.45)	.703	0.93 (0.59 - 1.49)	.771	0.80 (0.49 - 1.30)	.370	0.87 (0.55 - 1.37)	.538
Cardiovascular	1.57 (0.99 - 2.50)	.056	1.49 (0.92 - 2.39)	.103	1.58 (0.96 - 2.62)	.075	1.47 (0.93 - 2.33)	.100
NAR infections	0.65 (0.37 - 1.14)	.131	0.63 (0.35 - 1.11)	.111	0.64 (0.35 - 1.16)	.142	0.62 (0.35 - 1.09)	.094
Bone events	1.28 (0.69 - 2.38)	.433	1.38 (0.75 - 2.53)	.303	1.46 (0.74 - 2.91)	.276	1.32 (0.72 - 2.43)	.368
Renal events *	0.43 (0.17 - 1.09)	.075	0.44 (0.17 - 1.11)	.082	0.38 (0.14 - 0.99)	.047	0.40 (0.16 - 1.02)	.055

^aCox regression analysis was performed for comparison of the HR of overall death between responders and non-responders. Fine and Gray regression analysis was performed for comparison of the HR of events in the presence of competing risks.

^b*Adjusted for age, sex, prior AIDS-defining conditions (yes vs. no), HIV transmission category (injection drug users vs. non-injection drug users), nadir CD4+ cell count, cART (yes vs. no), undetectable HIV-RNA at baseline (yes vs. no), FIB4 \geq 3.25 (yes vs. no), genotype (3 vs. other genotypes), and exposure to abacavir, didanosine, indinavir, and lopinavir (lower than or equal to the median cumulative exposure in years vs higher than the median cumulative exposure).*

* Excluding 47 and 4 patients with diabetes mellitus and chronic renal failure at baseline, respectively

Abbreviations: HR, hazard ratio; CI, confidence interval; sHR, subhazard ratio; LR, liver-related; NLR, non-liver-related; AR, AIDS-related; NAR, non-AIDS-related; HCC, hepatocellular carcinoma.

Description of the 4 types of analysis

- **Primary analysis:** those who achieved sustained viral response with retreatment were included in the sustained viral response group
- **Second analysis:** the follow-up of retreated patients was censored on the same day as the initiation of the second course with interferon plus ribavirin.
- **Third analysis:** patients who were retreated were excluded from the analysis.
- **Fourth analysis:** treatment response status was considered a time-dependent variable