In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

PPD

Post-marketing safety analyses for multiple marketed products in collaboration with the D:A:D study

August 2017

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I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study 206247.

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RESEARCH QUESTION AND OBJECTIVE(S)

Specific Aims:

1. To describe any safety issues that arise among hepatically-impaired individuals exposed to ABC containing products (Ziagen®, Kivexa® or Trizivir®) and Telzir®.
2. To determine the risk of carcinogenicity following exposure to Ziagen®, Kivexa®, Trizivir® and Combivir®.
3. To determine the risk of hepatotoxicity and ischaemic cardiac events following exposure to Celsentri®.
4. To determine the risk of hepatotoxicity and ischaemic cardiac events in those exposed to Telzir®.

The D:A:D Study

This is a retrospective analysis of prospectively collected data from the D:A:D study. The D:A:D Study was an observational study of >49,000 HIV-1-positive patients from 11 cohorts from Europe, Australia, and the United States. The primary study aim was to investigate associations between the use of antiretroviral (ART) drugs and the risk of cardiovascular disease (CVD) and other major disease events. Data were collected prospectively during routine clinic visits; the standardised dataset includes information on socio-demographic factors (including ethnicity which is captured as part of individual cohort data collection processes, where permitted), AIDS events and deaths, known risk factors for CVD, laboratory markers for monitoring HIV (including CD4 count and HIV RNA) and CVD, liver and kidney function markers, ART and treatments that influence CVD risk. Enrolment in the D:A:D study took place in three phases: enrolment cohort I (enrolment from 1999-2000); enrolment cohort II (added in 2004); and enrolment cohort III (added in 2009).

All participants were under active follow-up in their cohorts at the time of enrolment in the D:A:D study and were seen for D:A:D clinical assessment at least every 8 months (depending on clinical need). Each participating cohort submitted an annual electronic dataset to the D:A:D Co-ordinating centre. Information on all incident cases of non-AIDS clinical events (including myocardial infarction [MI], stroke, cancers, end-stage liver and renal disease and deaths) were reported to the study co-ordinating centre via case reporting forms which captured detailed information about the event and related circumstances. Study personnel (at the co-ordinating centre and at local sites) received extensive training in the identification of events and completion of the event forms. Once the event form had been received, each event was validated (with dialogue between the co-ordinating centre and local site to clarify any discrepancies or queries) and coded using standardised criteria; validation and coding was performed blind to information on the patient's ART status. Routine site monitoring was carried out to limit the number of potentially missed events and ensure completeness of submitted data.

A full manual of operations (MOOP) and Standard Operating Procedures for the D:A:D study can be accessed on the D:A:D website PPD These provide full details of the data management procedures as well as formats for data submission.

Ethics, consent and permissions

All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review.

By the time of Merger 17 (at the time when data collection ceased), the study had captured data from 49,706 HIV-positive persons with a total follow-up of 467,477 PYRS from 11 different cohorts. Among this cohort, the study has information on 5372 deaths, 1191 MIs, 2794 cancer events (877

AIDS-defining, 1917 non-AIDS defining), 2002 new diagnoses of diabetes, 569 strokes, 432 ESLD and 131 ESRD events.

Statistical Methods

Specific statistical methods are described separately for each of the four study aims. However, in general, individuals were followed prospectively from enrolment in D:A:D (or the start of follow-up for specific non-CVD endpoints) to the date of the first of each clinical event, the date of death, six months after a patient's last clinic visit or 1st February 2016, whichever occurred first. Depending on the study aim, additional censoring may be applied to individual follow-up times (see relevant sections).

Where time-updated assessments of exposure to ART are reported, each person's follow-up was divided into a series of consecutive one-month periods, and a patient's cumulative exposure to the relevant drug/combination was calculated at the start of each period. Cumulative exposure includes, where appropriate, any exposure to treatment before enrolment/D:A:D baseline. This information is then used to assign the patient-month (and any events that occur during that month) to the appropriate exposure category. In a similar way, each person's covariate data is also updated at the start of each month, permitting time-varying analyses.

Exposure definitions

The D:A:D study does not capture information on specific co-formulations. Therefore, participants exposed to Ziagen®, Kivexa®, Trizivir® and Combivir® are identified as follows:

Ziagen®: Any person whose current regimen includes ABC but not 3TC or AZT, regardless of other drugs in the regimen.

Kivexa®: Any person whose current regimen includes ABC and 3TC but not AZT, regardless of other drugs in the regimen.

Trizivir®: Any person whose current regimen includes ABC, lamivudine (3TC) and zidovudine (AZT), regardless of other drugs in the regimen.

Combivir®: Any person whose current regimen includes AZT and 3TC but not ABC, regardless of other drugs in the regimen.

This will ensure that at any point in time, individuals can only be assigned to one of the four combinations (although individuals may switch from one of the combinations to another over time).

AIM 1: Analysis to describe the safety issues that arise among hepatically-impaired individuals exposed to Ziagen, Kivexa, Trizivir and Telzir

Specific methods

All D:A:D participants who had evidence of co-infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) and/or chronic liver enzyme elevations (CLEE – see definition below) at the time of initiating one of the four treatments/combinations are included in these analyses. For analyses of each drug, eligible participants were divided into three groups:

- HCV positive and/or HBV positive but with no evidence of CLEE
- HCV negative and HBV negative but with evidence of CLEE
- HCV positive and/or HBV positive and with evidence of CLEE

Individuals were then followed for the development of several clinical endpoints:

- End stage liver disease (ESLD) or Hepatocellular cancer (HCC)
- Cardiovascular disease (CVD) – MI, invasive coronary procedure, stroke or cardiac death (death due to definite/possible MI or other ischemic heart disease and sudden cardiac death). Note that, for obvious reasons, baseline CVD did not include cardiac death.
- Diabetes
- Other cancer (any cancer excluding HCC)
- End stage renal disease (ESRD)
- Mortality (classified as AIDS defining malignancies (ADM), liver, CVD, non-AIDS defining malignancies (NADM), other known causes of deaths, unknown causes of death)

Exclusion criteria: Participants from cohorts that do not provide information on alanine aminotransaminase (ALT) levels were excluded as were those whose date of first ALT assessment post-dated the start of each treatment/combination.

CLEE was defined as in the D:A:D paper by Kovari et al. (1) as ALT levels greater than the ULN (males/females >50/>35 U/L) at $\geq$2 visits spanning at least 6 months within 2 years. We used the date of the first elevated ALT as the event date. A single normal ALT measurement between 2 elevated values was permitted and therefore did not signal the end of a period of CLEE. HCV infection was defined by HCV seropositivity or detectable HCV RNA. HBV infection was defined by a positive HBV surface antigen, HBV e antigen, HBV core antibodies, or detectable HBV DNA.

Due to the estimated small number of study participants with ESLD, HCC and/or CLEE, and the possibility that the antiretroviral drugs may themselves induce hepatic impairment or liver enzyme elevation, the groups were defined at the time of first exposure to the treatment/combination and were not updated when an individual's status changed (e.g. if his/her ALT levels fall or if the individual subsequently becomes co-infected with HCV/HBV). Dosing levels for the relevant products were not available for any D:A:D participants.

Results

Of the 49,706 study participants, 945 were included in the Ziagen analysis with median (interquartile range (IQR)) follow-up of 1.25 (0.33-3.70) years, 4,173 were included in the Kivexa analysis with median (IQR) follow-up of 2.15 (0.63-4.82) years, 1,579 were included in the Trizivir analysis with median (IQR) follow-up of 0.78 (0.29-2.33) years, and 645 were included in the Telzir analysis with median (IQR) follow-up of 2.20 (0.76-4.91) years.

Table 1.1: Characteristics (frequency (%)) of D:A:D study participants with evidence of HBV/HCV and/or CLEE at time of initiating Ziagen

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Ziagen	945	100.0	408	100.0	244	100.0	293	100.0
HCV positive	589	62.3	328	80.4	-	-	261	89.1
HBV positive	157	16.6	108	26.5	-	-	49	16.7
CLEE	537	56.8	-	-	244	100.0	293	100.0
CVD at baseline[&&]	34	3.6	16	3.9	7	2.9	11	3.8
Diabetes at baseline	56	5.9	20	4.9	20	8.2	16	5.5
Other cancers at baseline[$$]	1	0.1	-	-	1	0.4	-	-
ESRD at baseline	9	1.0	4	1.0	-	-	5	1.7
Male	690	73.0	311	76.2	177	72.5	202	68.9
Cohort								
PPD	150	15.9	57	14.0	42	17.2	51	17.4
	52	5.5	18	4.4	18	7.4	16	5.5
	70	7.4	34	8.3	8	3.3	28	9.6
	165	17.5	68	16.7	32	13.1	65	22.2
	15	1.6	10	2.5	1	0.4	4	1.4
	418	44.2	191	46.8	121	49.6	106	36.2
	2	0.2	-	-	1	0.4	1	0.3
	47	5.0	22	5.4	7	2.9	18	6.1
	26	2.8	8	2.0	14	5.7	4	1.4
BMI (kg/m^2) at baseline								
<18	52	5.5	27	6.6	4	1.6	21	7.2
≥18, ≤26	668	70.7	300	73.5	165	67.6	203	69.3
>26, ≤30	118	12.5	41	10.1	43	17.6	34	11.6
>30	31	3.3	8	2.0	11	4.5	12	4.1
Unknown	76	8.0	32	7.8	21	8.6	23	7.9
Smoking status at baseline								
Current	476	50.4	233	57.1	67	27.5	176	39.8
Ex-smoker	235	24.9	99	24.3	65	26.6	71	24.0
Never smoked	198	21.0	61	15.0	102	41.8	35	29.6
Unknown	36	3.8	15	3.7	10	4.1	11	6.6
AIDS at baseline	353	37.4	143	35.1	98	40.2	112	38.6
Lipodystrophy at baseline	461	48.8	146	35.8	156	63.9	159	42.8
VL ≤50 copies/ml at baseline	269	28.5	75	18.4	89	36.5	105	28.4
Use of lipid-lowering drugs at baseline	108	11.4	29	7.1	54	22.1	25	11.9

[&&]CVD at baseline: MI or invasive coronary procedure or stroke before baseline date

[$$]Other cancers at baseline: Any AIDS or non-AIDS cancer excluding HCC

Table 1.2: Characteristics (median (IQR)) of D:A:D study participants at time of initiating Ziagen

	All participants			HBV/HCV infection only			CLEE only			HBV/HCV infection AND CLEE		
Baseline variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	41	38	46	40	36	44	44	39	51	42	39	46
CD4 (cells/mm^3)	337	199	524	301	163	462	388	252	585	345	210	515
Log_{10} RNA (copies/ml)	3.2	1.7	4.4	3.7	2.3	4.7	3.0	1.7	4.3	2.7	1.7	4.1
Systolic BP (mm/Hg)	120	112	130	120	110	130	125	120	138	120	110	130
Diastolic BP (mm/Hg)	80	70	81	80	70	80	80	70	87	80	70	80
Total cholesterol (mmol/l)	4.7	3.9	5.5	4.5	3.7	5.4	5.2	4.4	6.0	4.5	3.6	5.2
HDL cholesterol (mmol/l)	1.1	0.9	1.3	1.0	0.8	1.3	1.1	0.9	1.3	1.0	0.9	1.3
Triglyceride (mmol/l)	1.7	1.1	2.8	1.6	1.1	2.5	2.2	1.4	3.5	1.6	1.1	2.4
Haemoglobin (mmol/l)	8.8	8.0	9.4	8.7	7.9	9.4	8.9	8.3	9.5	8.8	7.8	9.4
Glucose (mmol/l)	5.1	4.6	5.7	5.0	4.4	5.5	5.2	4.7	5.9	5.1	4.6	5.8
Creatinine (micromol/l)	77	65	91	75	67	88	80	63	94	75	63	90
Bilirubin (micromol/l)	10	7	15	10	7	15	10	7	14	11	7	18
Albumin (gm/l)	41	38	44	41	36	44	44	41	46	41	38	43
ALT (IU/L)	45	27	78	32	20	62	46	30	64	65	39	107
AST (IU/L)	38	26	65	33	23	52	34	25	51	56	36	103

Table 1.3: Clinical events including deaths, over follow-up, after initiating Ziagen

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Ziagen	945	100.0	408	100.0	244	100.0	293	100.0
Clinical event								
ESLD/HCC	5	0.5	1	0.3	1	0.4	3	1.0
ESLD	4	0.4	1	0.3	1	0.4	2	0.7
HCC	1	0.1	-	-	-	-	1	0.3
CVD[££]	21	2.2	10	2.5	6	2.5	5	1.7
Diabetes	17	1.8	7	1.7	8	3.3	2	0.7
Other cancers[$$]	15	1.6	3	0.7	5	2.1	7	2.4
ESRD	4	0.4	1	0.3	1	0.4	2	0.7
Causes of death								
Any death	33	3.5	20	4.9	2	0.8	11	3.8
AIDS defining malignancies	5	0.5	3	0.7	-	-	2	0.7
Liver	10	1.1	5	1.2	1	0.4	4	1.4
Cardiovascular	2	0.2	2	0.5	-	-	-	-
Non-AIDS defining malignancies	4	0.4	2	0.5	1	0.4	1	0.3
Other known	9	1.0	5	1.2	-	-	4	1.4
Other unknown	3	0.3	3	0.7	-	-	-	-

[££]Cardiovascular disease: MI or invasive coronary procedure or stroke or cardiac death (death due to definite or possible MI; [$$]Other cancers: Any AIDS or non-AIDS cancer excluding HCC

Table 1.4: Characteristics (frequency (%)) of D:A:D study participants with evidence of HBV/HCV and/or CLEE at time of initiating Kivexa

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Kivexa	4173	100.0	1013	100.0	1693	100.0	1467	100.0
HCV positive	2115	50.7	781	77.1	-	-	1334	90.9
HBV positive	524	5.9	283	27.9	-	-	241	16.4
CLEE	3160	35.8	-	-	1693	100.0	1467	100.0
CVD at baseline[&&]	137	3.3	36	3.6	60	3.5	41	2.8
Diabetes at baseline	317	7.6	49	4.8	157	9.3	111	7.6
Other cancers at baseline[$$]	-	-	-	-	-	-	-	-
ESRD at baseline	29	0.7	12	1.2	7	0.4	10	0.7
Male	2923	70.1	749	73.9	1174	69.3	1000	68.2
Cohort								
PPD	1015	24.3	189	18.7	482	28.5	344	23.5
	477	11.4	132	13.0	222	13.1	123	8.4
	311	7.5	82	8.1	104	6.1	125	8.5
	430	10.3	109	10.8	166	9.8	155	10.6
	69	1.7	23	2.3	12	0.7	34	2.3
	1318	31.6	373	36.8	477	28.2	468	31.9
	37	0.9	8	0.8	22	1.3	7	0.5
	368	8.8	62	6.1	128	7.6	178	12.1
	148	3.6	35	3.5	80	4.7	33	2.6
BMI (kg/m^2) at baseline								
<18	212	5.1	71	7.0	47	2.8	94	6.4
≥18, ≤26	2890	69.3	734	72.5	1078	63.7	1078	73.5
>26, ≤30	641	15.4	109	10.8	357	21.1	175	11.9
>30	225	5.4	35	3.5	142	8.4	48	3.3
Unknown	205	4.9	64	6.3	69	4.1	72	4.9
Smoking status at baseline								
Current	1833	43.9	533	52.6	482	28.5	818	55.8
Ex-smoker	1213	29.1	250	24.7	529	31.3	434	29.6
Never smoked	934	22.4	172	17.0	588	34.7	174	11.9
Unknown	193	4.6	58	5.7	94	5.6	41	2.8
AIDS at baseline	1362	32.6	359	35.4	476	28.1	527	35.9
Lipodystrophy at baseline	1984	47.5	400	39.5	875	51.7	709	48.3
VL ≤50 copies/ml at baseline	2666	63.9	506	50.0	1225	72.4	935	63.7
Use of lipid-lowering drugs at baseline	697	16.7	105	10.4	441	26.1	151	10.3

[&&]CVD at baseline: MI or invasive coronary procedure or stroke before baseline date

[$$]Other cancers at baseline: Any AIDS or non-AIDS cancer excluding HCC

Table 1.5: Characteristics (median (IQR)) of D:A:D study participants at time of initiating Kivexa

	All participants			HBV/HCV infection only			CLEE only			HBV/HCV infection AND CLEE		
Baseline variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	45	40	51	43	38	49	47	41	54	45	40	50
CD4 (cells/mm^3)	473	294	692	375	219	577	550	378	770	447	285	655
Log_{10}RNA (copies/ml)	1.7	1.7	2.9	1.7	1.7	3.9	1.7	1.7	1.9	1.7	1.7	2.8
Systolic BP (mm/Hg)	122	115	134	120	110	130	126	119	137	120	112	130
Diastolic BP (mm/Hg)	80	70	85	80	70	80	80	70	86	80	70	83
Total cholesterol (mmol/l)	4.8	4.0	5.6	4.7	3.9	5.5	5.1	4.4	6.0	4.4	3.6	5.2
HDL cholesterol (mmol/l)	1.2	0.9	1.5	1.2	0.9	1.5	1.2	1.0	1.5	1.1	0.9	1.5
Triglyceride (mmol/l)	1.6	1.1	2.4	1.5	1.1	2.3	1.7	1.1	2.7	1.5	1.1	2.3
Haemoglobin (mmol/l)	8.8	8.0	9.5	8.6	7.6	9.4	9.0	8.2	9.6	8.8	8.1	9.5
Glucose (mmol/l)	5.2	4.7	5.9	5.2	4.6	5.8	5.3	4.8	5.9	5.2	4.7	5.8
Creatinine (micromol/l)	79	65	96	79	65	96	80	67	97	76	63	94
Bilirubin (micromol/l)	10	7	16	10	7	16	9	6	14	11	7	17
Albumin (gm/l)	42	39	45	41	37	44	43	40	46	42	38	45
ALT (IU/L)	39	25	65	28	20	47	38	26	56	52	31	89
AST (IU/L)	34	25	53	30	23	47	31	24	41	45	31	75

Table 1.6: Clinical events including deaths, over follow-up, after initiating Kivexa

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Kivexa	4173	100.0	1013	100.0	1693	100.0	1467	100.0
Clinical event								
ESLD/HCC	41	0.5	3	0.3	5	0.3	33	2.3
ESLD	31	0.4	2	0.2	5	0.3	24	1.6
HCC	12	0.2	1	0.1	-	-	11	0.8
CVD[££]	86	2.5	23	2.3	35	2.1	28	1.9
Diabetes	61	1.3	10	1.0	29	1.7	22	1.5
Other cancers[$$]	81	2.3	27	2.7	26	1.5	28	1.9
ESRD	12	0.3	1	0.1	1	0.1	10	0.7
Causes of death								
Any death	136	3.3	41	4.1	27	1.6	68	4.6
AIDS defining malignancies	18	0.4	7	0.7	6	0.4	5	0.3
Liver	30	0.7	6	0.6	-	-	24	1.6
Cardiovascular	12	0.3	3	0.3	5	0.3	4	0.3
Non-AIDS defining malignancies	22	0.5	6	0.6	4	0.2	12	0.8
Other known	39	0.9	12	1.2	9	0.5	18	1.2
Other unknown	15	0.4	7	0.7	3	0.2	5	0.3

[££]Cardiovascular disease: MI or invasive coronary procedure or stroke or cardiac death (death due to definite or possible MI

[$$]Other cancers: Any AIDS or non-AIDS cancer excluding HCC

Table 1.7: Characteristics (frequency (%)) of D:A:D Study participants with evidence of HBV/HCV and/or CLEE at the time of initiating Trizivir

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Trizivir	1579	100.0	586	100.0	530	100.0	463	100.0
HCV positive	859	54.4	444	75.8	-	-	415	89.6
HBV positive	260	16.5	180	30.7	-	-	80	17.3
CLEE	993	62.9	-	-	530	100.0	463	100.0
CVD at baseline[&&]	35	2.2	14	2.4	13	2.5	8	1.7
Diabetes at baseline	89	5.6	24	4.1	39	7.4	26	5.6
Other cancers at baseline[$$]	-	-	-	-	-	-	-	-
ESRD at baseline	5	0.3	-	-	1	0.2	4	0.9
Male	1115	70.6	429	73.2	372	70.2	314	67.8
Cohort								
PPD	134	8.5	56	9.6	44	8.3	34	7.3
	406	25.7	101	17.2	192	36.2	113	24.4
	155	9.8	60	10.2	48	9.1	47	10.2
	229	14.5	102	17.4	63	11.9	64	13.8
	5	0.3	1	0.2	3	0.6	1	0.2
	362	22.9	161	27.5	89	16.8	112	24.2
	16	1.0	1	0.2	13	2.5	2	0.4
	206	13.1	86	14.7	47	8.9	73	15.8
	66	4.2	18	3.1	31	5.9	17	3.7
BMI (kg/m^2) at baseline								
<18	76	4.8	41	7.0	8	1.5	27	5.8
≥18, ≤26	1078	68.3	418	71.3	331	62.5	329	71.1
>26, ≤30	234	14.8	67	11.4	114	21.5	53	11.5
>30	87	5.5	15	2.6	54	10.2	18	3.9
Unknown	104	6.6	45	7.7	23	4.3	36	7.8
Smoking status at baseline								
Current	696	44.1	311	53.1	150	28.3	235	50.8
Ex-smoker	423	26.8	137	23.4	156	29.4	130	28.1
Never smoked	328	20.8	103	17.6	166	31.3	59	12.7
Unknown	132	8.4	35	6.0	58	10.9	39	8.4
AIDS at baseline	477	30.2	193	32.9	149	28.1	135	29.2
Lipodystrophy at baseline	561	35.5	175	29.9	208	39.3	178	38.4
VL ≤50 copies/ml at baseline	795	50.4	218	37.2	335	63.2	242	52.3
Use of lipid-lowering drugs at baseline	217	13.7	40	6.8	135	25.5	42	9.1

[&&]CVD at baseline: MI or invasive coronary procedure or stroke before baseline date

[$$]Other cancers at baseline: Any AIDS or non-AIDS cancer excluding HCC

Table 1.8: Characteristics (median (IQR)) of D:A:D study participants with evidence of HBV/HCV and/or CLEE at the time of initiating Trizivir

	All participants			HBV/HCV infection only			CLEE only			HBV/HCV infection AND CLEE		
Baseline variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	43	38	50	41	36	47	46	39	55	43	38	50
CD4 (cells/mm^3)	451	257	690	350	199.5	589	555	362	770	441	264	684
Log_{10}RNA (copies/ml)	1.7	1.7	4.1	2.8	1.7	4.5	1.7	1.7	3.0	1.7	1.7	3.9
Systolic BP (mm/Hg)	120	112	132	120	110	130	125	115	137	120	115	130
Diastolic BP (mm/Hg)	80	70	81	78	70	80	80	70	85	78	70	80
Total cholesterol (mmol/l)	4.7	3.9	5.6	4.6	3.9	5.5	5.1	4.4	5.9	4.4	3.6	5.2
HDL cholesterol (mmol/l)	1.1	0.9	1.4	1.1	0.9	1.4	1.2	0.9	1.5	1.1	0.9	1.4
Triglyceride (mmol/l)	1.6	1.1	2.4	1.5	1.0	2.3	1.7	1.1	2.6	1.4	1.0	2.1
Haemoglobin (mmol/l)	8.8	8.0	9.5	8.6	7.9	9.3	9.0	8.2	9.6	8.9	8.1	9.6
Glucose (mmol/l)	5.1	4.6	5.8	5.0	4.5	5.8	5.2	4.7	5.9	5.1	4.7	5.8
Creatinine (micromol/l)	78	65	92	75	63	90	79	68	93	78	66	91
Bilirubin (micromol/l)	9	6	15	9	7	14	9	6	14	10	7	15
Albumin (gm/l)	42	39	45	40	37	44	43	40	46	42	39	45
AST (IU/L)	40	24	67	30	19	51	40	27	59	59	36	92
AST (IU/L)	34	25	55	30	22	48	31	24	43	50	31	82

Table 1.9: Clinical events, including deaths, over follow-up, after initiating Trizivir

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Trizivir	1579	100.0	586	100.0	530	100.0	463	100.0
Clinical event								
ESLD/HCC	6	0.2	1	0.2	1	0.2	4	0.9
ESLD	4	0.1	1	0.2	-	-	3	0.7
HCC	2	0.1	-	-	1	0.2	1	0.2
CVD[££]	23	1.8	13	2.2	6	1.1	4	0.9
Diabetes	12	1.1	4	0.7	7	1.3	1	0.2
Other cancers[$$]	20	1.3	10	1.7	6	1.1	4	0.9
End stage renal disease	-	-	-	-	-	-	-	-
Causes of death								
Any death	33	2.1	19	3.2	5	0.9	9	1.9
AIDS defining malignancies	4	0.3	2	0.3	1	0.2	1	0.2
Liver	4	0.2	1	0.2	-	-	3	0.7
Cardiovascular	3	0.2	3	6.6	-	-	-	-
Non-AIDS defining malignancies	5	0.3	3	13.2	2	0.4	-	-
Other known	12	0.8	6	24.0	1	0.2	5	1.1
Other unknown	5	0.3	4	13.2	1	0.2	-	-

[££]Cardiovascular disease: MI or invasive coronary procedure or stroke or cardiac death (death due to definite or possible MI

[$$]Other cancers: Any cancer AIDS or non-AIDS excluding HCC

Table 1.10: Characteristics (frequency (%)) of D:A:D Study participants with evidence of HBV/HCV and/or CLEE at the time of initiating Telzir

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Telzir	645	100.0	176	100.0	194	100.0	275	100.0
HCV positive	378	58.6	126	71.6	-	-	252	91.6
HBV positive	105	16.3	60	34.1	-	-	45	16.4
CLEE	469	72.7	-	-	194	100.0	275	100.0
CVD at baseline[&&]	25	3.9	4	2.3	11	5.7	10	3.6
Diabetes at baseline	44	6.8	9	5.1	17	8.8	18	6.6
Other cancers at baseline[$$]	-	-	-	-	-	-	-	-
ESRD at baseline	2	0.3	2	1.1	-	-	-	-
Male	466	72.3	130	73.9	133	68.6	203	73.8
Cohort								
PPD	96	14.9	22	12.5	32	16.5	42	15.3
	34	5.3	8	4.6	14	7.2	12	4.4
	101	15.7	37	21.0	16	8.3	48	17.5
	148	23.0	34	19.3	48	24.7	66	24.0
	4	0.6			4	2.1		
	139	21.6	27	15.3	26	13.4	86	31.3
	123	19.1	48	27.3	54	27.8	21	7.6
BMI (kg/m^2) at baseline	42	6.5	13	7.4	5	2.6	24	8.7
<18	473	73.3	126	71.6	147	75.8	200	72.7
≥18, ≤26	81	12.6	21	11.9	26	13.4	34	12.4
>26, ≤30	32	5.0	7	4.0	14	7.2	11	4.0
>30	17	2.6	9	5.1	2	1.0	6	2.2
Unknown								
Smoking status at baseline	336	52.1	93	52.8	72	37.1	171	62.2
Current	160	24.8	38	21.6	57	29.4	65	23.6
Ex-smoker	140	21.7	40	22.7	63	32.5	37	13.5
Never smoked	9	1.4	5	2.8	2	1.0	2	0.7
Unknown								
AIDS at baseline	194	30.1	50	28.4	59	30.4	85	30.9
Lipodystrophy at baseline	302	46.8	71	40.3	102	52.6	129	46.9
VL ≤50 copies/ml at baseline	203	31.5	43	24.4	52	26.8	108	39.3
Use of lipid-lowering drugs at baseline	96	14.9	14	8.0	53	27.3	29	10.6

[&&]CVD at baseline: MI or invasive coronary procedure or stroke before baseline date

[$$]Other cancers at baseline: Any AIDS or non-AIDS cancer excluding HCC

Table 1.11: Characteristics (median (IQR)) of D:A:D study participants with evidence of HBV/HCV and/or CLEE at the time of initiating Telzir

	All participants			HBV/HCV infection only			CLEE only			HBV/HCV infection AND CLEE		
Baseline variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	43	39	48	43	38	48	44	38	49	43	40	47
CD4 (cells/mm^3)	340	206	506	300	160	420	343	202	522	372	221	544
Log_{10}RNA (copies/ml)	3.4	1.7	4.7	4.0	1.8	4.9	3.7	1.7	4.8	2.6	1.7	4.4
Systolic BP (mm/Hg)	120	110	130	120	110	130	120	112	130	120	110	130
Diastolic BP (mm/Hg)	80	70	80	77	70	80	80	70	80	80	70	80
Total cholesterol (mmol/l)	4.4	3.6	5.3	4.2	3.5	5.3	4.7	4.1	5.8	4.2	3.4	4.9
HDL cholesterol (mmol/l)	1.0	0.8	1.3	1.1	0.8	1.4	1.1	0.8	1.3	1.0	0.8	1.3
Triglyceride (mmol/l)	1.5	1.1	2.4	1.5	1.1	2.2	1.6	1.1	3.1	1.4	1.0	2.3
Haemoglobin (mmol/l)	8.7	7.9	9.4	8.6	7.7	9.2	8.8	8.0	9.4	8.8	7.9	9.5
Glucose (mmol/l)	5.1	4.6	5.6	5.0	4.6	5.4	5.1	4.7	5.7	5.1	4.6	5.6
Creatinine (micromol/l)	71	61	83	69	61	83	72	61	85	71	62	83
Bilirubin (micromol/l)	10	8	17	9	7	13	9	9	14	13	9	22
Albumin (gm/l)	41	37	44	41	37	44	43	41	46	40	36	43
ALT (IU/L)	42	27	75	32	23	50	37	25	56	60	38	102
AST (IU/L)	39	27	66	36	26	50	32	23	46	53	35	100

Table 1.12: Clinical events, including deaths, over follow-up, after initiating Telzir

	All participants		HBV/HCV infection only		CLEE only		HBV/HCV infection AND CLEE	
	n	%	n	%	n	%	n	%
Total receiving Telzir	645	100.0	176	100.0	194	100.0	275	100.0
Clinical event								
ESLD/HCC	16	2.5	4	2.3	2	1.0	10	3.6
ESLD	10	1.6	1	0.6	1	0.5	8	2.9
HCC	7	1.1	3	1.7	1	0.5	3	1.1
CVD[£££]	16	2.5	3	1.7	7	3.6	6	2.2
Diabetes	9	1.4	1	0.6	1	0.5	7	2.6
Other cancers[$$]	15	2.3	2	1.1	7	3.6	6	2.2
ESRD	2	0.3	1	0.6	-	-	1	0.4
Causes of death								
Any death	28	4.3	9	5.1	5	2.6	14	5.1
AIDS defining malignancies	2	0.3	2	1.1	-	-	-	-
Liver	12	1.9	1	0.6	2	1.0	9	3.3
Cardiovascular	2	0.3	-	-	1	0.5	1	0.4
Non-AIDS defining malignancies	5	0.8	2	1.1	2	1.0	1	0.4
Other known	4	0.6	1	0.6	-	-	3	1.1
Other unknown	3	0.5	3	1.7	-	-	-	-

[£££]Cardiovascular disease: MI or invasive coronary procedure or stroke or cardiac death (death due to definite or possible MI

[$$]Other cancers: Any cancer AIDS or non-AIDS excluding HCC

AIM 2: To determine the risk of carcinogenicity following exposure to Ziagen, Kivexa, Trizivir and Combivir

Specific Methods

All D:A:D participants without a prior cancer at D:A:D study enrolment who are enrolled from cohorts that provide data on cancer incidence were included. Individuals known to have died or lost-to-follow-up before the cohort-specific baseline date for cancer analyses (2004 onwards) were excluded. Follow-up was from the latest of D:A:D entry or cohort-specific baseline date for cancer, until the first new cancer over prospective follow-up, with follow-up censored at the time of a competing cancer event.

Cancer events considered were:

- Any malignancy
- Any AIDS-defining malignancy (ADM)
- Kaposi's sarcoma (men only)
- Non-Hodgkin's lymphoma
- Cervical cancer (women only)
- Any non-AIDS-defining malignancy (NADM)
- Lung cancer
- Anal cancer (men only)
- Hodgkin's lymphoma
- Head and neck cancer

The incidence of each cancer (as a first cancer event) was calculated according to level of exposure to each of the four treatments/combinations (no exposure, 0-2 years, 2-4 years, 4-6 years, 6-8 years, 8-10 years and >10 years) and strata-specific event rates were calculated for each outcome. For each type of cancer, Poisson regression analyses was used to estimate the unadjusted relative rates for the different exposure categories; for events with sufficient numbers (all cancers, AIDS cancers, non-AIDS cancers and lung cancers), multivariable analyses were also fitted with adjustment for: gender, cohort, mode of HIV acquisition, ethnic group, calendar year, smoking status, HCV and HBV co-infection (all as categorical covariates), age and cumulative exposure to each drug (continuous covariates). Note that adjusted analyses do not include adjustment for factors that are thought to lie on the causal pathway between ART exposure and cancer development, including CD4 count.

Results

Of the 49,706 participants in the study, 39,928 were included in this analysis. Of these 2,417 experienced at least one episode of cancer in 345,524 person-years [PY, event rate (95% confidence interval), 0.700 (0.672-0.727) /100 PY], 756 experienced at least one AIDS-defining cancer (ADM) in 350,597 PY [0.215 (0.200-0.231)], and 1,661 experienced at least one non-AIDS defining cancer (NADM) in 349,096 PY [0.476 (0.453-0.499)]. Among the specific cancers, 332 experienced Kaposi's sarcoma in 325,285 PY [0.094 (0.084-0.104)], 362 experienced non-Hodgkin lymphoma in 352,755 PY [0.103 (0.092-0.113)], 62 experienced cervical cancer in 353,895 PY [0.018 (0.013-0.022)], 149 experienced anal cancer in 353,549 PY [0.042 (0.035-0.049)], 144 experienced Hodgkin lymphoma in 352,540 PY [0.041 (0.034-0.048)] and 144 experienced head and neck cancer in 353,673 PY [0.041 (0.034-0.047)]. Tables 2.1, 2.3, 2.5, 2.7, 2.8, 2.9, 2.10, 2.12 and 2.13 show the unadjusted rates and rate ratios for associations between each drug/combination and the different outcomes; Tables 2.2, 2.4, 2.6 and 2.11 show the adjusted estimates for those cancers with a sufficient number of endpoints to permit a robust analysis. With the exception of an increased risk of some cancers in those exposed to Ziagen for <2 years, very few clear trends were seen with increasing exposure to any drug. Given the multiple statistical tests that have been performed, and the lack of a clear dose-response trend, it is likely that these findings reflect a chance finding.

Table 2.1: Event rates (/100 person-years) and relative rate for any cancer, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment/ combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
Ziagen	No exposure	2131	314675	0.677	0.648	0.706	1.00	-	-	.	<0.001
	<2 years	157	15652	1.003	0.846	1.160	1.48	1.26	1.74	<0.001	
	≥2, <4	55	6419	0.857	0.630	1.083	1.27	0.97	1.65	0.09	
	≥4, <6	40	4089	0.978	0.675	1.281	1.44	1.06	1.97	0.02	
	≥6, <8	19	2330	0.815	0.491	1.273	1.20	0.77	1.89	0.42	
	≥8, <10	8	1305	0.613	0.265	1.208	0.91	0.45	1.81	0.78	
	≥10	7	1054	0.664	0.267	1.368	0.98	0.47	2.06	0.96	
Kivexa	No exposure	1867	275635	0.677	0.647	0.708	1.00	-	-	.	0.06
	<2 years	247	31144	0.793	0.694	0.892	1.17	1.03	1.34	0.02	
	≥2, <4	123	16382	0.751	0.618	0.884	1.11	0.92	1.33	0.27	
	≥4, <6	78	10322	0.756	0.588	0.923	1.12	0.89	1.40	0.34	
	≥6, <8	56	6647	0.842	0.622	1.063	1.24	0.95	1.62	0.11	
	≥8, <10	32	3266	0.980	0.640	1.319	1.45	1.02	2.05	0.04	
	≥10	14	2127	0.658	0.360	1.104	0.97	0.57	1.64	0.91	
Combivir	No exposure	1141	161172	0.708	0.667	0.749	1.00	-	-	.	0.24
	<2 years	577	79146	0.729	0.670	0.789	1.03	0.93	1.14	0.57	
	≥2, <4	233	37076	0.628	0.548	0.709	0.89	0.77	1.02	0.10	
	≥4, <6	164	26649	0.615	0.521	0.710	0.87	0.74	1.02	0.09	
	≥6, <8	128	18579	0.689	0.570	0.808	0.97	0.81	1.17	0.77	
	≥8, <10	92	12335	0.746	0.593	0.898	1.05	0.85	1.30	0.63	
	≥10	82	10568	0.776	0.608	0.944	1.10	0.88	1.37	0.42	
Trizivir	No exposure	2067	296119	0.698	0.668	0.728	1.00	-	-	.	0.80
	<2 years	163	21732	0.750	0.635	0.865	1.07	0.92	1.26	0.38	
	≥2, <4	77	10287	0.749	0.581	0.916	1.07	0.85	1.35	0.55	
	≥4, <6	48	7895	0.608	0.436	0.780	0.87	0.65	1.16	0.34	
	≥6, <8	35	4868	0.719	0.481	0.957	1.03	0.74	1.44	0.86	
	≥8, <10	15	2518	0.596	0.333	0.983	0.85	0.51	1.42	0.54	
	≥10	12	2105	0.570	0.295	0.996	0.82	0.46	1.44	0.48	

Table 2.2: Results from multivariable Poisson regression models to estimate adjusted relative rates for any cancer type, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

		Adjusted for demographic and cardiovascular factors[&&]					Further adjusted for other ART drugs in regimen				
Treatment/ combination	Duration of exposure	RR	95% CI		P-value	Global p-value	RR	95% CI		P-value	Global p-value
			Lower	Upper				Lower	Upper		
Ziagen	No exposure	1.00	-	-	.	0.01	1.00	-	-	.	0.06
	<2 years	1.40	1.18	1.64	<0.001		1.32	1.11	1.57	0.001	
	≥2, <4	1.17	0.89	1.53	0.26		1.09	0.83	1.44	0.54	
	≥4, <6	1.33	0.97	1.82	0.07		1.23	0.89	1.69	0.21	
	≥6, <8	1.11	0.71	1.75	0.64		1.02	0.64	1.62	0.93	
	≥8, <10	0.84	0.42	1.68	0.62		0.74	0.37	1.50	0.40	
	≥10	0.99	0.47	2.08	0.98		0.86	0.40	1.85	0.71	
Kivexa	No exposure	1.00	-	-	.	0.34	1.00	-	-	.	0.72
	<2 years	1.10	0.96	1.26	0.15		1.07	0.94	1.23	0.32	
	≥2, <4	1.07	0.89	1.29	0.48		1.02	0.85	1.23	0.82	
	≥4, <6	1.09	0.87	1.37	0.45		1.02	0.81	1.29	0.86	
	≥6, <8	1.18	0.90	1.54	0.23		1.09	0.82	1.44	0.56	
	≥8, <10	1.41	0.99	2.01	0.06		1.31	0.91	1.89	0.15	
	≥10	0.92	0.54	1.56	0.75		0.83	0.48	1.43	0.51	
Combivir	No exposure	1.00	-	-	.	0.06	1.00	-	-	.	0.30
	<2 years	1.04	0.94	1.15	0.48		1.01	0.90	1.12	0.91	
	≥2, <4	0.87	0.76	1.01	0.06		0.86	0.73	1.00	0.05	
	≥4, <6	0.83	0.71	0.98	0.03		0.82	0.68	1.00	0.04	
	≥6, <8	0.88	0.73	1.06	0.18		0.87	0.69	1.09	0.23	
	≥8, <10	0.89	0.72	1.10	0.29		0.87	0.66	1.14	0.31	
	≥10	0.92	0.74	1.16	0.48		0.85	0.62	1.18	0.34	
Trizivir	No exposure	1.00	-	-	.	0.41	1.00	-	-	.	0.26
	<2 years	1.01	0.86	1.18	0.91		0.99	0.84	1.16	0.91	
	≥2, <4	1.03	0.82	1.29	0.83		1.00	0.80	1.26	0.98	
	≥4, <6	0.77	0.58	1.02	0.07		0.74	0.55	0.99	0.04	
	≥6, <8	0.90	0.65	1.26	0.55		0.86	0.61	1.22	0.40	

≥8, <10	0.76	0.46	1.26	0.29	0.71	0.42	1.19	0.19
≥10	0.76	0.43	1.34	0.34	0.67	0.37	1.20	0.18

[&&] Adjusted for: age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, smoking status, HCV and HBV infection

Table 2.3: Event rates (/100 person-years) and relative rate for AIDS-defining cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment/ combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI		P-value	Global p-value
					Lower	Upper		Lower	Upper		
Ziagen	No exposure	697	318978.65	0.219	0.202	0.235	1.00	-	-	.	0.02
	<2 years	42	16009.88	0.262	0.183	0.342	1.20	0.88	1.64	0.25	
	≥2, <4	8	6581.25	0.122	0.052	0.239	0.56	0.28	1.12	0.10	
	≥4, <6	5	4192.36	0.119	0.039	0.278	0.55	0.23	1.32	0.18	
	≥6	4	4834.77	0.083	0.023	0.212	0.38	0.14	1.01	0.05	
Kivexa	No exposure	648	279096.83	0.232	0.214	0.250	1.00	-	-	.	<0.001
	>2 years	68	31731.37	0.214	0.163	0.265	0.92	0.72	1.19	0.53	
	≥2 years	21	16765.84	0.125	0.072	0.179	0.54	0.35	0.83	0.01	
	≥2, <4	9	10581.52	0.085	0.039	0.162	0.37	0.19	0.71	0.00	
	≥4, <6	6	6833.92	0.047	0.017	0.103	0.38	0.17	0.84	0.02	
	≥6	4	5587.42	0.072	0.020	0.183	0.31	0.12	0.82	0.02	
Combivir	No exposure	452	163180.87	0.277	0.251	0.303	1.00	-	-	.	<0.001
	<2 years	191	80321.4	0.238	0.204	0.272	0.27	0.13	0.53	<0.001	
	≥2, <4	56	37653.03	0.149	0.110	0.188	0.86	0.72	1.02	0.08	
	≥4, <6	31	27047.39	0.115	0.074	0.155	0.54	0.41	0.71	<0.001	
	≥6, <8	12	18884.11	0.064	0.033	0.111	0.41	0.29	0.60	<0.001	
	≥8, <10	6	12641.68	0.047	0.017	0.103	0.23	0.13	0.41	<0.001	
	≥10	8	10868.43	0.100	0.043	0.198	0.17	0.08	0.38	<0.001	
Trizivir	No exposure	669	300429.94	0.223	0.206	0.240	1.00	-	-	.	<0.001
	<2 years	50	22085.66	0.226	0.164	0.289	1.02	0.76	1.36	0.91	
	≥2, <4	22	10416.19	0.211	0.123	0.299	0.95	0.62	1.45	0.81	
	≥4, <6	8	7977.85	0.100	0.031	0.170	0.45	0.22	0.90	0.02	
	≥6	7	9687.25	0.072	0.019	0.126	0.32	0.15	0.68	0.003	

Table 2.4: Results from multivariable Poisson regression models to estimate adjusted relative rates for AIDS defining cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

		Adjusted for demographic and cardiovascular factors[&&]					Further adjusted for other ART drugs in regimen				
Treatment/ combination	Duration of exposure	RR	95% CI		P-value	Global p-value	RR	95% CI		P-value	Global p-value
			Lower	Upper				Lower	Upper		
Ziagen	No exposure	1.00	-	-	.	0.06	1.00	-	-	.	0.004
	<2 years	1.35	0.98	1.85	0.07		1.68	1.21	2.35	0.002	
	≥2, <4	0.61	0.30	1.24	0.17		0.65	0.32	1.32	0.24	
	≥4, <6	0.61	0.25	1.48	0.27		0.62	0.25	1.51	0.29	
	≥6, <8	0.54	0.20	1.44	0.21		0.47	0.17	1.30	0.15	
Kivexa	No exposure	1.00	-	-	.	0.07	1.00	-	-	.	0.04
	<2 years	1.10	0.86	1.42	0.45		1.20	0.93	1.55	0.17	
	≥2, <4	0.70	0.45	1.08	0.10		0.71	0.46	1.11	0.13	
	≥4, <6	0.52	0.27	1.01	0.06		0.50	0.25	0.98	0.04	
	≥6, <8	0.63	0.28	1.43	0.27		0.59	0.26	1.35	0.21	
	≥8	0.61	0.23	1.65	0.33		0.56	0.20	1.56	0.27	
Combivir	No exposure	1.00	-	-	.	<0.001	1.00	-	-	.	0.01
	<2 years	0.92	0.77	1.09	0.35		1.21	1.00	1.45	0.05	
	≥2, <4	0.57	0.43	0.76	<0.001		0.84	0.61	1.16	0.29	
	≥4, <6	0.44	0.31	0.64	<0.001		0.72	0.47	1.12	0.15	
	≥6, <8	0.24	0.13	0.42	<0.001		0.45	0.23	0.87	0.02	
	≥8, <10	0.18	0.08	0.41	<0.001		0.39	0.16	0.98	0.04	
	≥10	0.36	0.18	0.74	0.005		0.84	0.35	2.05	0.70	
Trizivir	No exposure	1.00	-	-	.	0.01	1.00	-	-	.	0.19
	<2 years	1.01	0.76	1.35	0.94		1.12	0.84	1.50	0.45	
	≥2, <4	0.89	0.58	1.36	0.59		1.04	0.67	1.62	0.85	
	≥4, <6	0.44	0.22	0.88	0.02		0.55	0.27	1.12	0.10	
	≥6, <8	0.42	0.20	0.89	0.02		0.55	0.25	1.23	0.15	

[&&] Adjusted for: age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, smoking status, HCV and HBV infection

Table 2.5: Event rates (/100 person-years) and relative rate for incidence of non-AIDS-defining cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment /combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI		P-value	Global p-value
					Lower	Upper		Lower	Upper		
Ziagen	No exposure	1434	317982	0.451	0.428	0.474	1.00	-	-	.	<0.001
	<2 years	115	15836	0.726	0.593	0.859	1.61	1.33	1.95	<0.001	
	≥2, <4	47	6451	0.729	0.520	0.937	1.62	1.21	2.16	0.001	
	≥4, <6	35	4109	0.852	0.570	1.134	1.89	1.35	2.64	<0.001	
	≥6, <8	16	2340	0.684	0.349	1.019	1.52	0.93	2.48	0.10	
	≥8, <10	7	1310	0.534	0.215	1.100	1.18	0.56	2.49	0.65	
	≥10	7	1068	0.656	0.264	1.351	1.45	0.69	3.06	0.32	
Kivexa	No exposure	1219	278366	0.438	0.413	0.462	1.00	-	-	.	<0.001
	<2 years	179	31582	0.567	0.484	0.650	1.29	1.11	1.51	0.001	
	≥2, <4	102	16584	0.615	0.496	0.734	1.40	1.15	1.72	0.001	
	≥4, <6	69	10418	0.662	0.506	0.819	1.51	1.19	1.93	0.001	
	≥6, <8	50	6706	0.746	0.539	0.952	1.70	1.28	2.26	<0.001	
	≥8, <10	28	3300	0.848	0.534	1.163	1.94	1.33	2.82	0.001	
	≥10	14	2140	0.654	0.358	1.098	1.49	0.88	2.53	0.14	
Combivir	No exposure	689	163214	0.422	0.391	0.454	1.00	-	-	.	0.007
	<2 years	386	79965	0.483	0.435	0.531	1.14	1.01	1.30	0.04	
	≥2, <4	177	37394	0.473	0.404	0.543	1.12	0.95	1.32	0.17	
	≥4, <6	133	26841	0.496	0.411	0.580	1.17	0.97	1.41	0.09	
	≥6, <8	116	18667	0.621	0.508	0.734	1.47	1.21	1.79	<0.001	
	≥8, <10	86	12403	0.693	0.547	0.840	1.64	1.31	2.06	<0.001	
	≥10	74	10611	0.697	0.538	0.856	1.65	1.30	2.10	<0.001	
Trizivir	No exposure	1398	299269	0.467	0.443	0.492	1.00	-	-	.	0.16
	<2 years	113	22005	0.514	0.419	0.608	1.10	0.91	1.33	0.33	
	≥2, <4	55	10362	0.531	0.390	0.671	1.14	0.87	1.49	0.35	
	≥4, <6	40	7944	0.504	0.347	0.660	1.08	0.79	1.48	0.64	
	≥6, <8	32	4878	0.656	0.429	0.883	1.40	0.99	1.99	0.06	
	≥8, <10	11	2529	0.435	0.217	0.778	0.93	0.51	1.69	0.81	
	≥10	12	2109	0.569	0.294	0.994	1.22	0.69	2.15	0.50	

Table 2.6: Results from multivariable Poisson regression models to estimate adjusted relative rates for any non-AIDS cancer, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

		Adjusted for demographic and cardiovascular factors[&&]					Further adjusted for other ART drugs in regimen				
Treatment/ combination	Duration of exposure	RR	95% CI		P-value	Global p-value	RR	95% CI		P-value	Global p-value
			Lower	Upper				Lower	Upper		
Ziagen	No exposure	1.00	-	-	.	0.001	1.00	-	-	.	0.06
	<2 years	1.42	1.17	1.72	<0.001		1.26	1.03	1.54	0.02	
	≥2, <4	1.39	1.04	1.86	0.03		1.30	0.96	1.75	0.08	
	≥4, <6	1.63	1.16	2.29	0.004		1.54	1.09	2.18	0.01	
	≥6, <8	1.27	0.77	2.07	0.35		1.23	0.75	2.04	0.41	
	≥8, <10	0.94	0.45	1.98	0.87		0.92	0.43	1.96	0.83	
	≥10	1.18	0.56	2.48	0.66		1.20	0.56	2.57	0.64	
Kivexa	No exposure	1.00	-	-	.	0.06	1.00	-	-	.	0.11
	<2 years	1.10	0.94	1.29	0.23		1.06	0.90	1.24	0.47	
	≥2, <4	1.20	0.98	1.47	0.08		1.19	0.97	1.46	0.10	
	≥4, <6	1.28	1.00	1.63	0.05		1.28	1.00	1.65	0.05	
	≥6, <8	1.30	0.98	1.74	0.07		1.31	0.98	1.76	0.07	
	≥8, <10	1.50	1.03	2.20	0.03		1.51	1.03	2.23	0.04	
	≥10	1.05	0.62	1.80	0.84		1.07	0.62	1.85	0.80	
Combivir	No exposure	1.00	-	-	.	0.14	1.00	-	-	.	0.81
	<2 years	1.12	0.99	1.27	0.08		0.98	0.86	1.11	0.72	
	≥2, <4	1.07	0.90	1.26	0.46		0.93	0.78	1.12	0.45	
	≥4, <6	1.08	0.89	1.30	0.44		0.94	0.76	1.16	0.55	
	≥6, <8	1.26	1.04	1.54	0.02		1.06	0.83	1.35	0.65	
	≥8, <10	1.27	1.01	1.59	0.04		1.00	0.75	1.34	0.99	
	≥10	1.16	0.91	1.47	0.24		0.84	0.59	1.19	0.32	
Trizivir	No exposure	1.00	-	-	.	0.85	1.00	-	-	.	0.70
	<2 years	0.99	0.82	1.21	0.95		0.96	0.79	1.17	0.72	
	≥2, <4	1.11	0.85	1.45	0.46		1.06	0.81	1.40	0.65	
	≥4, <6	0.93	0.68	1.27	0.63		0.87	0.63	1.20	0.38	
	≥6, <8	1.12	0.79	1.59	0.52		1.02	0.71	1.47	0.92	

≥8, <10	0.72	0.40	1.31	0.28	0.65	0.35	1.19	0.16
≥10	0.90	0.51	1.59	0.71	0.78	0.43	1.42	0.42

[&&] Adjusted for: age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, smoking status, HCV and HBV infection

Table 2.7: Event rates (/100 person-years) and relative rate for Kaposi's sarcoma, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment/ combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
Ziagen	No exposure	315	320498.62	0.098	0.087	0.109	1.00	-	-	.	<0.001
	<2 years	14	16108.93	0.087	0.048	0.146	0.88	0.52	1.51	0.65	
	≥2	3	15677.59	0.019	0.004	0.056	0.19	0.06	0.61	0.005	
Kivexa	No exposure	294	280331.88	0.105	0.093	0.117	1.00	-	-	.	<0.001
	<2 years	26	31926.74	0.081	0.050	0.113	0.78	0.52	1.16	0.22	
	≥2, <4	6	16888.54	0.036	0.013	0.077	0.34	0.15	0.76	0.01	
	≥4	6	23137.97	0.026	0.010	0.056	0.25	0.11	0.55	<0.001	
Combivir	No exposure	229	164018.6	0.140	0.122	0.158	1.00	-	-	.	<0.001
	<2 years	62	80815.31	0.077	0.058	0.096	0.55	0.42	0.73	<0.001	
	≥2, <4	22	37807.86	0.058	0.034	0.083	0.42	0.27	0.65	<0.001	
	≥4, <6	14	27120.87	0.052	0.028	0.087	0.37	0.22	0.63	<0.001	
	≥6	5	42522.48	0.012	0.004	0.027	0.08	0.03	0.20	<0.001	
Trizivir	No exposure	289	301958.28	0.096	0.085	0.107	1.00	-	-	.	<0.001
	<2 years	27	22161.21	0.122	0.076	0.168	1.27	0.86	1.89	0.23	
	≥2, <4	11	10450.82	0.105	0.053	0.188	1.10	0.60	2.01	0.76	
	≥4	5	17714.82	0.028	0.009	0.066	0.29	0.12	0.71	0.01	

Table 2.8: Event rates (/100 person-years) and relative rate for Non-Hodgkin lymphoma, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment/ combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
Ziagen	No exposure	328	321005	0.102	0.091	0.113	1.00	-	-	.	0.49
	<2 years	21	16127	0.130	0.075	0.186	1.27	0.82	1.98	0.28	
	≥2, <4	7	6590	0.106	0.043	0.219	1.04	0.49	2.20	0.92	
	≥4	6	9033	0.066	0.024	0.145	0.65	0.29	1.46	0.30	
Kivexa	No exposure	303	280786	0.108	0.096	0.120	1.00	1.00	1.00	.	0.01
	<2 years	36	32007	0.112	0.076	0.149	1.04	0.74	1.47	0.81	
	≥2, <4	12	16864	0.071	0.031	0.111	0.66	0.37	1.17	0.16	
	≥4	11	23098	0.048	0.019	0.076	0.44	0.24	0.81	0.01	
Combivir	No exposure	198	164484	0.120	0.104	0.137	1.00	1.00	1.00	.	<0.001
	<2 years	109	80724	0.135	0.110	0.160	1.12	0.89	1.42	0.34	
	≥2, <4	27	37845	0.071	0.044	0.098	0.59	0.40	0.89	0.01	
	≥4, <6	14	27190	0.051	0.025	0.078	0.43	0.25	0.74	0.002	
	≥6, <8	8	18918	0.042	0.018	0.083	0.35	0.17	0.71	0.004	
	≥8	6	23593	0.025	0.009	0.055	0.21	0.09	0.48	<0.001	
Trizivir	No exposure	327	302277	0.108	0.096	0.120	1.00	1.00	1.00	.	0.02
	<2 years	20	22296	0.090	0.050	0.129	0.83	0.53	1.30	0.42	
	≥2, <4	6	10480	0.057	0.021	0.125	0.53	0.24	1.19	0.12	
	≥4	9	17702	0.051	0.023	0.097	0.47	0.24	0.91	0.03	

Table 2.9: Event rates and relative rate for cervical cancer, stratified by whether or not the participant had ever been exposed Ziagen, Kivexa, Combivir and Trizivir

Treatment/ combination	Exposure	Events	PYRS	Rate / 100 years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
Ziagen	No exposure	54	322048	0.017	0.012	0.021	1.00	-	-		0.31
	<2 years	8	31847	0.025	0.011	0.049	1.50	0.71	3.15	0.29	
Kivexa	No exposure	51	281633	0.018	0.013	0.023	1.00	-	-		0.69
	<2 years	6	32137	0.019	0.007	0.041	1.03	0.44	2.40	0.94	
	≥2	5	40124	0.012	0.004	0.029	0.69	0.27	1.72	0.43	
Combivir	No exposure	25	165124	0.015	0.009	0.021	1.00	-	-		0.38
	<2 years	20	81062	0.025	0.014	0.035	1.63	0.91	2.93	0.10	
	≥2, <4	7	37942	0.018	0.007	0.038	1.22	0.53	2.82	0.64	
	≥4	10	69766	0.014	0.007	0.026	0.95	0.45	1.97	0.88	
Trizivir	No exposure	53	303353	0.017	0.013	0.022	1.00	-	-		0.96
	>0 years	9	50542	0.018	0.008	0.034	1.02	0.50	2.07	0.96	

Table 2.10: Event rates (/100 person-years) and relative rate for incidence of lung cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment /combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI		P-value	Global p-value
					Lower	Upper		Lower	Upper		
Ziagen	No exposure	244	321969	0.076	0.066	0.085	1.00	-	-	.	0.05
	<2 years	13	16178	0.080	0.043	0.137	1.06	0.61	1.85	0.84	
	≥2, <4	10	6592	0.152	0.073	0.279	2.00	1.06	3.77	0.03	
	≥4, <6	8	4207	0.190	0.082	0.375	2.51	1.24	5.07	0.01	
	≥6	6	4853	0.124	0.045	0.269	1.63	0.73	3.67	0.24	
Kivexa	No exposure	214	281577	0.076	0.066	0.086	1.00	-	-	.	0.36
	<2 years	24	32144	0.075	0.045	0.105	0.98	0.64	1.50	0.93	
	≥2, <4	18	16949	0.106	0.063	0.168	1.40	0.86	2.26	0.17	
	≥4, <6	14	10658	0.131	0.072	0.220	1.73	1.01	2.97	0.05	
	≥6, <8	5	6868	0.073	0.024	0.170	0.96	0.39	2.32	0.92	
	≥8, <10	6	5603	0.107	0.039	0.233	1.41	0.63	3.17	0.41	
	≥10	9	10894	0.083	0.038	0.157	1.09	0.55	2.15	0.80	
Combivir	No exposure	125	165052	0.076	0.062	0.089	1.00	-	-	.	0.93
	<2 years	65	81067	0.080	0.061	0.100	1.06	0.78	1.43	0.71	
	≥2, <4	33	37919	0.087	0.057	0.117	1.15	0.78	1.69	0.48	
	≥4, <6	19	27209	0.070	0.042	0.109	0.92	0.57	1.49	0.74	
	≥6, <8	17	18959	0.090	0.052	0.144	1.18	0.71	1.97	0.51	
	≥8	13	12699	0.102	0.055	0.175	1.35	0.76	2.39	0.30	
Trizivir	No exposure	228	303275	0.075	0.065	0.085	1.00	-	-	.	0.19
	<2 years	19	22335	0.085	0.051	0.133	1.13	0.71	1.81	0.60	
	≥2, <4	10	10481	0.095	0.046	0.175	1.27	0.67	2.39	0.46	
	≥4, <6	11	8022	0.137	0.068	0.245	1.82	1.00	3.34	0.05	
	≥6, <8	8	4973	0.161	0.069	0.317	2.14	1.06	4.33	0.03	
	≥8	5	4713	0.106	0.034	0.248	1.41	0.58	3.42	0.45	

Table 2.11: Results from multivariable Poisson regression models to estimate adjusted relative rates for lung cancer, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

		Adjusted for demographic and cardiovascular factors[&&]					Further adjusted for other ART drugs in regimen				
Treatment/ combination	Duration of exposure	RR	95% CI		P-value	Global p-value	RR	95% CI		P-value	Global p-value
			Lower	Upper				Lower	Upper		
Ziagen	No exposure	1.00	-	-	.	0.11	1.00	-	-	.	0.17
	<2 years	0.96	0.54	1.68	0.87		0.95	0.54	1.70	0.87	
	≥2, <4	1.75	0.92	3.32	0.09		1.77	0.92	3.41	0.09	
	≥4, <6	2.31	1.14	4.70	0.02		2.25	1.08	4.70	0.03	
	≥6	1.62	0.71	3.66	0.25		1.51	0.63	3.61	0.36	
Kivexa	No exposure	1.00	-	-	.	0.63	1.00	-	-	.	0.66
	<2 years	0.89	0.59	1.37	0.61		0.87	0.57	1.33	0.52	
	≥2, <4	1.25	0.77	2.03	0.37		1.23	0.75	2.02	0.41	
	≥4, <6	1.62	0.94	2.80	0.08		1.60	0.91	2.83	0.10	
	≥6, <8	0.84	0.34	2.06	0.71		0.84	0.33	2.10	0.70	
	≥8, <10	1.43	0.53	3.89	0.48		1.36	0.48	3.81	0.56	
	≥10	1.03	0.25	4.19	0.97		0.95	0.23	4.03	0.95	
Combivir	No exposure	1.00	-	-	.	0.92	1.00	-	-	.	0.23
	<2 years	1.06	0.78	1.44	0.70		0.90	0.65	1.23	0.50	
	≥2, <4	1.09	0.74	1.60	0.68		0.83	0.55	1.27	0.40	
	≥4, <6	0.83	0.51	1.34	0.44		0.59	0.34	1.02	0.06	
	≥6, <8	0.96	0.57	1.59	0.86		0.61	0.33	1.12	0.11	
	≥8, <10	1.01	0.57	1.80	0.96		0.56	0.28	1.14	0.11	
	≥10	0.75	0.38	1.48	0.40		0.32	0.13	0.78	0.01	
Trizivir	No exposure	1.00	-	-	.	0.37	1.00	-	-	.	0.59
	<2 years	1.03	0.65	1.66	0.89		1.03	0.64	1.66	0.90	
	≥2, <4	1.25	0.66	2.36	0.50		1.23	0.65	2.34	0.53	
	≥4, <6	1.73	0.94	3.17	0.08		1.65	0.88	3.10	0.12	
	≥6, <8	1.85	0.91	3.76	0.09		1.66	0.79	3.50	0.18	

≥8	1.23	0.50	2.99	0.66		1.01	0.38	2.64	0.99

[&&] Adjusted for: age, gender, cohort, mode of HIV acquisition, ethnic group, calendar year, smoking status, HCV and HBV infection

Table 2.12: Event rates (/100 person-years) and relative rate for incidence of Anal cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment /combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
Ziagen	No exposure	124	321771	0.039	0.032	0.045	1.00	-	-	.	0.03
	<2 years	13	16142	0.081	0.043	0.138	2.09	1.18	3.70	0.01	
	≥2, <4	5	6585	0.076	0.025	0.177	1.97	0.81	4.82	0.14	
	≥4	7	9052	0.077	0.031	0.159	2.01	0.94	4.30	0.07	
Kivexa	No exposure	108	281425	0.038	0.031	0.046	1.00	-	-	.	0.19
	<2 years	15	32094	0.047	0.026	0.077	1.22	0.71	2.09	0.47	
	≥2, <4	9	16905	0.053	0.024	0.101	1.39	0.70	2.74	0.35	
	≥4, <6	7	10638	0.066	0.026	0.136	1.71	0.80	3.68	0.17	
	≥6	10	12488	0.080	0.038	0.147	2.09	1.09	3.99	0.03	
Combivir	No exposure	56	165003	0.034	0.025	0.043	1.00	-	-	.	0.03
	<2 years	30	81023	0.037	0.024	0.050	1.09	0.70	1.70	0.70	
	≥2, <4	28	37866	0.074	0.047	0.101	2.18	1.38	3.43	0.00	
	≥4, <6	12	27196	0.044	0.023	0.077	1.30	0.70	2.43	0.41	
	≥6, <8	9	18936	0.048	0.022	0.090	1.40	0.69	2.83	0.35	
	≥8	14	23525	0.060	0.033	0.100	1.75	0.98	3.15	0.06	
Trizivir	No exposure	127	303032	0.042	0.035	0.049	1.00	-	-	.	0.66
	<2 years	9	22333	0.040	0.018	0.077	0.96	0.49	1.89	0.91	
	≥2, <4	7	10468	0.067	0.027	0.138	1.60	0.75	3.41	0.23	
	≥4	6	17717	0.034	0.012	0.074	0.81	0.36	1.83	0.61	

Table 2.13: Event rates (/100 person-years) and relative rate for incidence of Hodgkin's lymphoma cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment /combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI		P-value	Global p-value
					Lower	Upper		Lower	Upper		
Ziagen	No exposure	125	321773	0.039	0.032	0.046	1.00	-	-	.	0.25
	<2 years	10	16134	0.062	0.030	0.114	1.60	0.84	3.04	0.16	
	≥2	9	15632	0.058	0.026	0.109	1.48	0.75	2.91	0.25	
Kivexa	No exposure	111	281433	0.039	0.032	0.047	1.00	-	-	.	0.45
	<2 years	18	32064	0.056	0.033	0.089	1.42	0.86	2.34	0.16	
	≥2, <4	8	16921	0.047	0.015	0.080	1.20	0.58	2.46	0.62	
	≥4	7	23121	0.030	0.012	0.062	0.77	0.36	1.65	0.50	
Combivir	No exposure	88	164888	0.053	0.042	0.065	1.00	-	-	.	0.001
	<2 years	33	80962	0.041	0.027	0.055	0.76	0.51	1.14	0.19	
	≥2, <4	9	37934	0.024	0.011	0.045	0.44	0.22	0.88	0.02	
	≥4, <6	5	27212	0.018	0.006	0.043	0.34	0.14	0.85	0.02	
	≥6	9	42543	0.021	0.010	0.040	0.40	0.20	0.79	0.01	
Trizivir	No exposure	125	303044	0.041	0.034	0.048	1.00	-	-	.	0.23
	<2 years	12	22295	0.054	0.028	0.094	1.30	0.72	2.36	0.38	
	≥2	7	28200	0.025	0.010	0.051	0.60	0.28	1.29	0.19	

Table 2.14: Event rates (/100 person-years) and relative rate for incidence of Head and neck cancers, stratified by duration of exposure to Ziagen, Kivexa, Combivir and Trizivir

Treatment /combination	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI		P-value	Global p-value
					Lower	Upper		Lower	Upper		
Ziagen	No exposure	122	321863	0.038	0.031	0.045	1.00	-	-	.	0.03
	<2 years	14	16155	0.087	0.047	0.145	2.29	1.32	3.98	0.003	
	≥2	8	15656	0.051	0.022	0.101	1.35	0.66	2.76	0.41	
Kivexa	No exposure	100	281473	0.036	0.029	0.042	1.00	-	-	.	0.03
	<2 years	24	32119	0.075	0.045	0.105	2.10	1.35	3.28	0.001	
	≥2, <4	9	16937	0.053	0.024	0.101	1.50	0.76	2.96	0.25	
	≥4, <6	6	10650	0.056	0.021	0.123	1.59	0.70	3.61	0.27	
	≥6	5	12494	0.040	0.013	0.093	1.13	0.46	2.77	0.80	
Combivir	No exposure	45	165070	0.027	0.019	0.035	1.00	-	-	.	0.01
	<2 years	38	81015	0.047	0.032	0.062	1.72	1.12	2.65	0.01	
	>2, <4	22	37901	0.058	0.034	0.082	2.13	1.28	3.55	0.004	
	>4, <6	16	27183	0.059	0.034	0.096	2.16	1.22	3.82	0.01	
	>6, <8	13	18934	0.069	0.037	0.117	2.52	1.36	4.67	0.003	
	>8, <10	10	23571	0.042	0.020	0.078	1.56	0.78	3.09	0.21	
Trizivir	No exposure	117	303169	0.039	0.032	0.046	1.00	-	-	.	0.43
	<2 years	12	22316	0.054	0.028	0.094	1.39	0.77	2.52	0.27	
	≥2, <4	7	10479	0.067	0.027	0.138	1.73	0.81	3.71	0.16	
	≥4	8	17710	0.045	0.020	0.089	1.17	0.57	2.40	0.67	

Aim 3: Analysis to describe the risk of hepatotoxicity and ischemic cardiac events following exposure to Celsentri.

Specific methods

For analyses of hepatotoxicity, participants were excluded if they had evidence of either ESLD or HCC at D:A:D study entry. For analyses of CLEE, participants were excluded if they had evidence of hepatotoxicity or CLEE at D:A:D study entry ; these analyses additionally excluded those from cohorts that did not provide data on ALT levels, those without any measured ALT, and those with <6 months of follow-up (the minimum time required in order to define CLEE). For analyses of ischemic events, participants were excluded if they had a prior MI at D:A:D study entry.

Cohort-specific baseline dates were chosen according to the introduction of routine ALT monitoring in the individual cohorts. All D:A:D participants without HBV and HCV infection, with ≥3 ALT measurements, ≥6 months of follow-up and normal ALT at baseline were followed from baseline to the earliest of CLEE, death, 6 months prior to a date of a first positive HCV/HBV test, 6 months after last visit, or February 1, 2016. The incidence of CLEE was defined as the number of first events divided by the total person years of follow-up (PYFU), with CLEE being defined as in Aim 1.

Four separate primary endpoints were considered:

- ESLD/HCC
- CLEE
- MI
- Composite endpoint of MI or sudden cardiovascular death

Participants were stratified according to whether or not they had ever received, or were currently receiving, Celsentri. As the total number of participants exposed to Celsentri is small, and the duration of exposure is generally short, no further stratification has been undertaken for duration of exposure to the drug. Where available, additional information has been provided on data captured at the time of hepatic disease. This includes possible biopsy, fibroscan and signs of hepatic decompensation (ascites, hepatorenal syndrome (HRS), hepatic encephalopathy grade 3 or 4 and oesophageal variceal bleeding).

The primary analyses consider an ALT-based definition of CLEE as ALT measurements are frequently assessed in most D:A:D cohorts. However, as a sensitivity analysis, we have also considered broadening the endpoint (CLEE-expanded) to incorporate a definition based on elevations in ALT *or* AST (>45/35 IU/L in men/women), total bilirubin (>25) and albumin (>48) levels; CLEE-expanded was defined on the earliest date when the individual met the criteria for CLEE based on any of these markers, and individuals were additionally excluded from these analyses if they had raised levels of AST, bilirubin or albumin at D:A:D study entry. However, these analyses should be interpreted with caution. Whilst AST values are available in a similar proportion of participants (91.4%), the frequency of assessment of AST is lower than that of ALT; the number of cohorts that provide data on albumin/bilirubin, as well as the frequency of measurements, are lower than for ALT, with only 70.4% of participants having at least one measured bilirubin value and 44.9% at least one measure albumin.

Finally, we considered the main predictors of CLEE whilst individuals were currently receiving Celsentri. Factors considered for inclusion in these analyses were those previously identified as being associated with CLEE in the paper by Kovari et al [1]. Age, gender and HCV/HBV status were included in a multivariable model, regardless of statistical significance. However, due to the relatively small number of endpoints available for this analysis, and the need to avoid over-fitted models, other covariates (CD4 count, calendar year, participating cohort, BMI, smoking status, viral load, hypertension, dyslipidaemia and lipodystrophy) were only included in multivariable models if they were significantly associated with the development of CLEE in univariate models, and retained their significance in the model after adjustment for the other covariates.

Results

Of the 49,706 participants in the D:A:D Study, 471/49 692 experienced ESLD/HCC, 10889/32451 experienced CLEE, 1108/49308 experienced MI, and 1134/49308 experienced the composite endpoint of

MI or cardiac death. A further 13534/28958 individuals met the criteria for CLEE-expanded. Table 3.1 shows the event rates stratified by whether or not the participant had ever been exposed to Celsentri; in Table 3.2, the follow-up time and events that occurred among those ever exposed were divided into follow-up time whilst currently receiving, or during previous exposure. The characteristics of participants who experienced each of the endpoints whilst currently receiving Celsentri are shown in Tables 3.3 and 3.4.

Of the 57 participants who experienced a CLEE whilst on Celsentri, 35 discontinued the drug. In an analysis of the predictors of CLEE development whilst on Celsentri, only younger age (global p=0.01, relative rate [95% confidence interval] compared to those aged <40 years: 40-50 years 0.96 [0.47-1.93]; >50 years 0.43 [0.20-0.90]) and HCV coinfection (p=0.02, 2.84 [1.22-6.60]) were associated with CLEE development in univariate analyses. In a multivariable analysis, including additional adjustment for gender and HBV status, only HCV co-infection (p=0.02, 3.16 [1.32-7.55]) remained significantly associated with the development of CLEE whilst on Celsentri.

Table 3.1: Event rates stratified by whether or not the participant had ever been exposed to Celsentri

Outcome	Never exposed to Celsentri			Ever exposed to Celsentri		
	Events	Follow-up	Rate /100 years of follow-up	Events	Follow-up	Rate /100 years of follow-up
ESLD/HCC	469	462056	0.102 (0.092, 0.111)	2	4524	0.088 (0.024, 0.226)
CLEE	10809	249113	4.339 (4.257, 4.422)	80	1998	4.004 (3.126, 4.881)
CLEE-expanded	13441	199190	6.748 (6.634, 6.862)	93	13838	6.700 (5.338, 8.062)
MI	1098	454095	0.248 (0.233, 0.262)	10	4293	0.233 (0.089, 0.377)
MI/cardiac death	1124	454095	0.248 (0.233, 0.262)	10	4293	0.233 (0.089, 0.377)

Table 3.2: Event rates further stratified by current or previous exposure (in those who had ever been exposed) to Celsentri

Outcome	Currently exposed to Celsentri			Previously exposed to Celsentri		
	Events	Follow-up	Rate /100 years of follow-up	Events	Follow-up	Rate /100 years of follow-up
ESLD/HCC	1	3390	0.029 (0.001, 0.164)	1	1133	0.088 (0.002, 0.492)
CLEE	57	1466	3.889 (2.880, 4.899)	23	533	4.315 (2.552, 6.079)
CLEE-expanded	61	1024	5.957 (4.462, 7.451)	32	364	8.793 (9.252, 11.823)
MI	7	3185	0.220 (0.088, 0.453)	3	1108	0.271 (0.056, 0.791)
MI/cardiac death	7	3185	0.220 (0.088, 0.453)	3	1108	0.271 (0.056, 0.791)

Table 3.3: Characteristics (frequency (%)) of D:A:D study participants who were currently receiving Celsentri and who experienced each clinical event

	ESLD/HCC		CLEE		CLEE-expanded		MI		MI /cardiac death	
	n	%	n	%	n	%	n	%	n	%
Total currently on Celsentri	1		57	100.0	61	100.0	7	100.0	7	100.0
Male	1		43	75.4	46	75.4	6	85.7	6	85.7
Age group (years)										
<20	-		-	-	-	-	-	-	-	-
≥20, ≤30	-		4	7.0	4	6.6	-	-	-	-
>30, ≤40	-		7	12.3	9	14.8	-	-	-	-
>40, ≤50	-		27	47.4	22	36.1	1	14.3	1	14.3
>50	1		19	33.3	26	42.6	6	85.7	6	85.7
Unknown	-		-	-	-	-	-	-	-	-
BMI (kg/m^2)										
<18	-		-	-	-	-	-	-	-	-
≥18, <26	1		38	66.7	38	62.3	6	85.7	6	85.7
≥26, <30	-		9	15.8	14	23.0	1	14.3	1	14.3
≥30	-		8	14.0	7	11.5	-	-	-	-
Unknown	-		2	3.5	2	3.3	-	-	-	-
Smoking										
Current	1		14	24.6	11	18.0	3	42.9	3	42.9
Ex-smoker	-		9	15.8	6	9.8	3	42.9	3	42.9
Never smoked	-		8	14.0	13	21.3	1	14.3	1	14.3
Unknown	-		26	45.6	31	50.8	-	-	-	-
CD4 count ($cells/mm^3$)										
≥500	-		17	29.8	16	26.2	3	42.9	3	42.9
<500, ≥350	1		7	12.3	6	9.8	1	14.3	1	14.3
<350, ≥200	-		6	10.5	7	11.5	2	28.6	2	28.6

<200, ≥100	-			1	1.6	1	14.3	1	14.3
<100	-	1	1.8	-	-	-	-	-	-
Unknown		26	45.6	31	50.8	-	-	-	-
VL ≤50 copies/ml	-	21	36.8	19	31.2	3	42.9	3	42.9
Diabetes	-	5	8.8	7	11.5	1	14.3	1	14.3
Dyslipidemia	-	19	33.3	21	34.4	6	85.7	6	85.7
Hypertension	-	11	19.3	12	19.7	2	28.6	2	28.6
Lipodystrophy	1	16	28.1	15	24.6	6	85.7	6	85.7
Cohort									
PPD	-	13	22.8	13	21.3	1	14.3	1	14.3
	-	9	15.8	12	19.7	-	-	-	-
	-	8	14.0	9	14.8	-	-	-	-
	1	6	10.5	4	6.6	1	14.3	1	14.3
	-	2	3.5	2	3.3	-	-	-	-
	-	17	29.8	17	27.9	3	42.9	3	42.9
	-	1	1.8	1	1.6	-	-	-	-
	-	-	-	2	3.3	-	-	-	-
	-	1	1.8	1	1.6	2	28.6	2	28.6

Table 3.4: Characteristics (median (IQR)) of D:A:D study participants who were currently receiving Celsentri and who experienced each clinical event

	ESLD/HCC			CLEE			CLEE-expanded			MI			MI/cardiac death		
Variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	51	51	51	46	42	51	48	42	57	58	52	63	58	52	63
CD4 (cells/mm^3)	596	596	596	513	362	709	511	332	737	486	233	856	486	233	856
Log_{10} RNA (copies/ml)	1.7	1.7	1.7	1.7	1.7	2.6	1.7	1.7	2.0	1.7	1.7	2.1	1.7	1.7	2.1
Systolic BP (mm/Hg)	130	130	130	130	115	138	123	115	139	130	120	145	130	120	145
Diastolic BP (mm/Hg)	70	70	70	80	70	87	80	70	85	83	80	90	83	80	90
Total cholesterol (mmol/l)	3.8	3.8	3.8	5.1	4.4	6.1	5.3	4.0	5.9	5.9	4.7	6.6	5.9	4.7	6.6
HDL cholesterol (mmol/l)	1.2	1.2	1.2	1.2	0.9	1.5	1.1	0.9	1.4	0.9	0.7	1.2	0.9	0.7	1.2
Triglyceride (mmol/l)	0.9	0.9	0.9	2.1	1.2	3.5	2.3	1.4	3.0	4.1	2.2	4.8	4.1	2.2	4.8
Haemoglobin (mmol/l)	9.1	9.1	9.1	8.7	8.1	9.9	8.9	8.3	9.4	9.7	9.4	9.8	9.7	9.4	9.8
Glucose (mmol/l)	4.6	4.6	4.6	5.3	4.6	5.9	5.0	4.4	5.3	6.2	5.6	6.4	6.2	5.6	6.4
Creatinine (micromol/l)	71	71	71	79	68	94	79	69	96	75	64	86	75	64	86
Bilirubin (micromol/l)	13	13	13	11	8	17	10	6	15	9	5	17	9	5	17
Albumin (gm/l)	42	42	42	41	39	45	41	39	43	48	46	49	48	46	49
ALT (IU/L)	64	64	64	28	23	39	25	20	33	18	15	21	18	15	21
AST (IU/L)	35	35	35	29	23	34	24	21	32	21	16	25	21	16	25

Table 3.5: List of participants who developed HCC/ESLD whilst on Celsentri

Patient ID	Celsentri start date	Date of HCC/ESLD	Biopsy	Fibroscan	Ascites	HRS	Hepatic encephalopathy	Variceal bleeding
PPD	02-Feb-09	19-Feb-14	No additional data available					

Aim 4: Analysis to describe the risk of hepatotoxicity and ischemic cardiac events following exposure to Telzir

Specific methods

These analyses follow the same statistical plan as was used for Aim 4, with Telzir replacing Censentri. Participants were stratified according to whether or not they have ever received, or are currently receiving, Telzir. Further stratification by exposure to Telzir has also been undertaken.

Results

Of the 49,706 participants in the D:A:D Study, 471/49 692 experienced ESLD/HCC, 10889/32451 experienced CLEE, 1108/49308 experienced MI, and 1134/49308 experienced the composite endpoint of MI or cardiac death. A further 13534/28958 individuals met the criteria for CLEE-expanded. Table 4.1 shows the event rates stratified by whether or not the participant had ever been exposed to Telzir. In Table 4.2, the follow-up time and events that occurred among those ever exposed were divided into follow-up time whilst currently receiving, or during previous exposure. The characteristics of participants who experienced each of the endpoints whilst current receiving Telzir are shown in Tables 4.3 and 4.4. Table 4.5 provides event rates further stratified by duration of exposure to Telzir. Whilst univariate analyses suggested an increased rate of ESLD/HCC in those with longer exposure to Telzir (consistent with previous analyses from the study (2)), this association was removed after adjustment for age, gender, HCV/HBV co-infection and exposure to other ART drugs. A small increased risk of the CLEE-expanded endpoint in those exposed to Telzir for <2 years, appeared to be driven largely by a small group of people who met the criteria for CLEE based on bilirubin elevations. Given that bilirubin is not measured routinely in all cohorts, it is likely that this is a result of more regular bilirubin monitoring in individuals who are perceived to be at increased risk of CLEE, including those with previous exposure to atazanavir.

Of the 92 participants who experienced a CLEE whilst on Telzir, 59 discontinued the drug. In an analysis of the predictors of CLEE development whilst on Telzir, HCV coinfection (p=0.001, relative rate [95% confidence interval]3.42 [1.93-6.07]), smoking status (global p=0.001, compared to never smokers: current smokers 1.47 [0.93-2.33]; ex-smokers 0.68 [0.36-1.27]), a current viral load $\leq$50 copies/ml (p=0.001, 2.47 [1.62-3.77]) and hypertension (p=0.04, 0.44 [0.20-0.96]) were each significantly associated with CLEE development in univariate analyses. Of these factors, only HCV co-infection (p=0.001, 3.25 [1.79-5.87]) and a current viral load $\leq$50 copies/ml (p=0.001, 2.40 [1.43-4.03]) remained significantly associated with the development of CLEE whilst on Telzir after adjustment (with the latter association most likely reflecting a greater frequency of monitoring in those engaged in care, rather than a causal association with an undetectable viral load).

Table 4.1: Event rates stratified by whether or not the participant had ever been exposed to Telzir

Outcome	Never exposed to Telzir			Ever exposed to Telzir		
	Events	Follow-up	Rate /100 years of follow-up	Events	Follow-up	Rate /100 years of follow-up
ESLD/HCC	432	453306	0.095 (0.086, 0.104)	39	13274	0.294 (0.202, 0.386)
CLEE	10606	244437	4.339 (4.256, 4.422)	283	6674	4.240 (3.746, 4.734)
CLEE-expanded	13178	195797	6.730 (6.616, 6.845)	356	4781	7.446 (6.673, 8.220)
MI	1070	445510	0.240 (0.226, 0.255)	38	12878	0.295 (0.201, 0.389)
MI/cardiac death	1096	445510	0.246 (0.231, 0.261)	38	12878	0.295 (0.201, 0.389)

Table 4.2: Event rate further stratified by current or previous exposure (in those who had ever been exposed) to Telzir

Outcome	Currently exposed to Telzir			Previously exposed to Telzir		
	Events	Follow-up	Rate /100 years of follow-up	Events	Follow-up	Rate /100 years of follow-up
ESLD/HCC	20	5344	0.374 (0.229, 0.578)	19	7930	0.240 (0.144, 0.374)
CLEE	92	2953	3.116 (2.479, 3.752)	191	3721	5.133 (4.405, 5.861)
CLEE-expanded	98	2315	4.233 (3.395, 5.071)	258	2466	10.464 (9.187, 11.741)
MI	17	5188	0.328 (0.191, 0.525)	21	7690	0.273 (0.156, 0.390)
MI/cardiac death	17	5188	0.328 (0.191, 0.525))	21	7690	0.273 (0.156, 0.390)

Table 4.3: Characteristics (frequency (%)) of D:A:D study participants who were currently receiving Telzir and experienced each clinical event

	ESLD/HCC		CLEE		CLEE-expanded		MI		MI/cardiac death	
	n	%	n	%	n	%	n	%	n	%
Total currently on Telzir	20	100.0	92	100.0	98	100.0	17	100.0	17	100.0
Male	18	100.0	70	76.1	74	75.5	16	94.1	16	94.1
Age group (years)										
<20	-	-	-	-	-	-	-	-	-	-
≥20, ≤30	-	-	6	6.5	7	7.1	-	-	-	-
>30, ≤40	-	-	24	26.1	23	23.5	2	11.8	2	11.8
>40, ≤50	12	60.0	38	41.3	40	40.8	4	23.5	4	23.5
>50	8	40.0	24	26.1	28	28.6	11	64.7	11	64.7
Unknown	-	-			-	-	-	-	-	-
BMI (kg/m^2)										
<18	4	20.0	4	4.4	4	4.1	1	5.9	1	5.9
≥18, <26	11	55.0	67	72.8	68	69.4	13	76.5	13	76.5
≥26, <30	3	15.0	15	16.3	18	18.4	1	5.9	1	5.9
≥30	2	10.0	4	4.4	5	5.1	-	-	-	-
Unknown	-	-	2	2.2	3	3.1	2	11.8	2	11.8
Smoking										
Current	12	60.0	28	30.4	24	24.5	11	64.7	11	64.7
Ex-smoker	6	30.0	12	13.0	15	15.3	4	23.5	4	23.5
Never smoked	2	10.0	23	25.0	27	27.6	2	11.8	2	11.8
Unknown	-	-	29	31.5	32	32.7	-	-	-	-
CD4 count ($cells/mm^3$)										
≥500	6	30.0	21	22.8	22	22.5	10	58.8	10	58.8
≥350, <500	3	15.0	13	14.1	11	11.2	2	11.8	2	11.8
≥200, <350	4	20.0	13	14.1	14	14.3	3	17.7	3	17.7
≥100, <200	5	25.0	15	16.3	14	14.3	-	-	-	-
<100	2	10.0	3	3.3	8	8.2	2	11.8	2	11.8
Unknown	-	-	27	29.4	29	29.6	-	-	-	-

VL ≤50 copies/ml	14	70.0	34	37.0	39	39.8	15	88.2	15	88.2
Diabetes	3	15.0	4	4.4	4	4.1	3	17.7	3	17.7
Dyslipidemia	15	75.0	32	34.8	34	34.7	15	88.2	15	88.2
Hypertension	11	55.0	7	7.6	6	6.1	1	41.2	1	41.2
Lipodystrophy	11	55.0	20	21.7	23	23.5	13	76.5	13	76.5
Cohort										
PPD	4	20.0	13	14.1	15	15.3	4	23.5	4	23.5
	1	5.0	-	-	1	1.0	1	5.9	1	5.9
	6	30.0	10	10.9	8	8.2	1	5.9	1	5.9
	4	20.0	19	20.7	26	26.5	5	29.4	5	29.4
	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-
	-	-	1	1.1	1	1.0	-	-	-	-
	4	20.0	9	9.8	4	4.1	1	5.9	1	5.9
	1	5.0	40	43.5	43	43.9	5	29.4	5	29.4

Table 4.4: Characteristics (median (IQR)) of D:A:D study participants who were currently receiving Telzir and experienced each clinical event

	ESLD/HCC			CLEE			CLEE-expanded			MI			MI/cardiac death		
Variables	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3
Age (years)	48	45	51	44	37	50	45	37	50	52	48	60	52	48	60
CD4 (cells/mm^3)	293	129	565	358	190	567	347	180	587	540	304	598	540	304	598
Log_{10} RNA (copies/ml)	1.7	1.7	2.0	1.7	1.7	3.1	1.7	1.7	2.9	1.7	1.7	1.7	1.7	1.7	1.7
Systolic BP (mm/Hg)	120	110	130	120	110	123	120	110	120	126	120	140	126	120	140
Diastolic BP (mm/Hg)	76	66	80	72	60	80	75	60	80	76	70	80	76	70	80
Total cholesterol (mmol/l)	3.8	2.7	5.6	4.7	4.2	5.6	4.7	4.0	5.5	5.8	5.3	7.6	5.8	5.3	7.6
HDL cholesterol (mmol/l)	0.9	0.6	1.3	1.3	0.9	1.5	1.1	0.9	1.4	1.1	0.9	1.3	1.1	0.9	1.3
Triglyceride (mmol/l)	1.4	1.0	2.4	1.8	1.1	2.4	1.6	1.1	2.3	2.1	1.5	3.6	2.1	1.5	3.6
Haemoglobin (mmol/l)	8.1	7.3	8.7	8.9	8.3	9.4	8.4	7.7	9.1	9.1	8.3	9.3	9.1	8.3	9.3
Glucose (mmol/l)	5.1	4.5	5.8	5.1	4.6	5.5	5.0	4.3	5.5	5.1	4.5	6.4	5.1	4.5	6.4
Creatinine (micromol/l)	68	60	98	69	58	83	72	53	81	89	65	96	89	65	96
Bilirubin (micromol/l)	18	10	27	9	7	10	9	7	10	9	6	12	9	6	12
Albumin (gm/l)	34	30	41	43	41	45	43	40	45	44	41	48	44	41	48
ALT (IU/L)	39	26	66	30	23	42	26	20	34	29	16	37	29	16	37
AST (IU/L)	68	43	103	27	22	33	26	21	31	25	22	34	25	22	34

Table 4.5: Event rates (/100 person-years) and relative rate for each of the outcomes, stratified by exposure to Telzir

Outcome	Duration of exposure	Events	Person-years	Rate /100 person-years	95% CI		Relative Rate	95% CI			Global p-value
					Lower	Upper		Lower	Upper	P-value	
ESLD/HCC	No exposure	432	453306	0.095	0.086	0.104	1.00	-	-	.	<0.001
	<2 years	16	7045	0.227	0.130	0.369	2.38	1.45	3.93	0.001	
	≥2, <4	9	3195	0.282	0.129	0.535	2.96	1.53	5.72	0.001	
	≥4	14	3034	0.461	0.252	0.774	4.84	2.84	8.25	<0.001	
CLEE	No exposure	10606	244437	4.339	4.256	4.422	1.00	-	-	.	0.70
	<2 years	165	3670	4.496	3.810	5.182	1.04	0.89	1.21	0.65	
	≥2, <4	62	1565	3.963	2.976	4.949	0.91	0.71	1.17	0.48	
	≥4	56	1439	3.891	2.872	4.910	0.90	0.69	1.17	0.42	
CLEE-expanded	No exposure	13178	195797	6.730	6.616	6.845	1.00	-	-	.	0.003
	<2 years	226	2634	8.580	7.461	9.699	1.27	1.12	1.45	<0.001	
	≥2, <4	66	1079	6.117	4.641	7.592	0.91	0.71	1.16	0.44	
	≥4	64	1068	5.994	4.525	7.462	0.89	0.70	1.14	0.36	
MI	No exposure	1070	44510	0.240	0.226	0.255	1.00	-	-	.	0.41
	<2 years	24	6896	0.348	0.209	0.487	1.45	0.97	2.17	0.07	
	≥2, <4	7	3066	0.228	0.092	0.470	0.95	0.45	2.00	0.89	
	≥4	7	2916	0.240	0.495	0.418	1.00	0.48	2.10	0.99	
CVD	No exposure	1096	445510	0.246	0.231	0.261	1.00	-	-	.	0.46
	<2 years	24	6896	0.348	0.209	0.487	1.41	0.94	2.12	0.09	
	≥2, <4	7	3066	0.228	0.092	0.470	0.93	0.44	1.95	0.84	
	≥4	7	2916	0.240	0.495	0.495	0.98	0.46	2.05	0.95	

Table 4.6: List of participants who developed HCC/ESLD whilst on Telzir (Data from CRFs: 1=yes, 0=no, 9=unknown)

Patient ID	Telzir start date	Date of HCC/ESLD	Biopsy	Fibroscan	Metavir stage	Ascites	HRS	Encephal opathy	Variceal bleeding	Liver transplant
PPD	14-Apr-04	21-Nov-06				No additional data available				
	17-Jul-06	01-Jul-07				No additional data available				
	17-Feb-06	19-May-08				No additional data available				
	19-Dec-03	27-Apr-15				No additional data available				
	13-Sep-11	01-Nov-13	0	0				1		
	02-Nov-04	09-Jan-07				No additional data available				
	07-Mar-07	05-Feb-15	1	1	3		1			
	20-Jun-06	06-Jun-11				No additional data available				
	27-Jul-10	19-Apr-11				No additional data available				
	15-Oct-04	23-Nov-07	1		4			1	1	
	03-Feb-10	04-Mar-10				No additional data available				
	13-Oct-04	12-Mar-13	1	1	3	1				
	06-Apr-05	14-Apr-07	9	9				1	1	
	29-Jun-05	23-Aug-13				No additional data available				
	30-Aug-05	26-Feb-14	0	0		1		1		
	20-Apr-06	19-Jun-11	0	9					1	
	02-Mar-05	15-Apr-13	0	0						1
	09-Feb-06	08-Aug-13	0	0		1		1		
	02-Feb-06	10-Apr-06	0	0				1		
	14-Oct-05	11-Oct-06	9	0				1		

Summary

As expected based on the known epidemiology of HIV in participating countries, the number of individuals who initiated treatment with Ziagen, Kivexa, Trizivir or Telzir who had evidence of HBV/HCV coinfection and/or CLEE was relatively small. Whilst clinical events were rare in these individuals, ESLD/HCC and death from liver-related causes were relatively common, as would be expected. We found no strong signals between exposure to Ziagen, Kivexa, Combivir or Trizivir with the development of cancer (neither overall, nor any specific cancer type); it is likely that a small increased risk of some cancers in those exposed to Ziagen for <2 years reflects a Type I error due to the number of statistical tests performed. Other associations with cancers were consistent with previous findings from the cohort (3). Relatively few individuals receiving Celsentri experienced a liver- or CVD-related outcome: HCV-coinfection was the primary predictor of CLEE in those on Celsentri and just under two-thirds of those experiencing CLEE whilst on Celsentri subsequently discontinued the drug. Our findings relating to individuals who received Telzir were broadly consistent with previous D:A:D findings, although with increased follow-up, the increased rate of ESLD/HCC in those with longer exposure to Telzir seen previously now appears to be explained by preferential use of the drug in those with known HCV/HBV co-infection, with the small increased risk of CLEE (based on an expanded definition only) among those exposed to Telzir for <2 years being largely explained by reported increases in bilirubin (a marker that is not measured routinely in all cohorts).

As with all analyses from the D:A:D study, we note the usual limitations of an observational study. In particular, whilst we have attempted to adjust for potential confounding factors wherever possible, the small number of participants in some analyses means that this has not always been possible. Thus, care should be taken when interpreting any findings to avoid making assumptions regarding causality. For the same reason, some of the reported analyses may be lacking power to detect significant association.

References

1. Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drugs and risk of chronic alanine aminotransferase elevation in human immunodeficiency virus (HIV)-monoinfected persons: the Data Collection on Adverse Events of Anti-HIV Drugs Study. Open Forum Infect Dis 2016; 3(1):ofw009 doi: 10.1093/ofid/ofw009.
2. Ryom L, Lundgren JD, De Wit S, et al. Use of antiretroviral therapy and risk of end-stage liver disease and hepatocellular carcinoma in HIV-positive persons. AIDS 2016; 30: 1731-43.
3. Bruyand M, Ryom L, Shepherd L, et al. Cancer risk and use of protease inhibitor or nonnucleoside reverse transcriptase inhibitor-based combination antiretroviral therapy: The D:A:D Study. J Aquir Immune Defic Syndr 2015; 68: 568-77.

TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Post-marketing safety analyses for multiple marketed products in collaboration with the D:A:D study

Compound Number:	GI265235, GSK2285967, GSK587048, GSK586135, UK427857, GW433908
Development Phase	IV
Effective Date:	19-APR-2017
Subject:	Post-marketing safety, Ziagen®, Kivexa®, Trizivir®, Combivir®, Celsentri®, Telzir®

Author(s):

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1. LIST OF ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
ADM	AIDS-defining malignancy
AEs	adverse events
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine transaminase
ARV	antiretroviral
AZT	zidovudine
cART	combination antiretroviral therapy
CLEE	chronic liver enzyme elevation
CV	cardiovascular
D:A:D	Data collection on Adverse events of anti-HIV Drugs
ESLD	end-stage liver disease
ESRD	end-stage renal disease
EU	European Union
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICP	invasive cardiovascular procedure
MI	myocardial infarction
NADM	non-AIDS-defining malignancy
PYRS	person years

Trademark Information

Trademarks of ViiV Healthcare and the GlaxoSmithKline group of companies
Ziagen®
Kivexa®
Trizivir®
Combivir®
Celsentri®
Telzir®

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[SAS]

2. **RESPONSIBLE PARTIES:** SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

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SPONSOR SIGNATORY:

Vani Vannappagari Primary Author/ Project officer	**Date**
Harmony Garges VP, Global Medical Sciences	**Date**
Nassrin Payvandi VP, Safety and Pharmacovigilance	**Date**

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: Caroline Sabin

Investigator Signature _____ Date _____

Investigator Name: Lene Ryom

Investigator Signature _____ Date _____

Investigator Name: David Kamara

Investigator Signature _____ Date _____

Investigator Name: Camilla Hatleberg

Investigator Signature _____ Date _____

3. ABSTRACT

ViiV Healthcare's pharmacovigilance strategy for the mature product portfolio is to monitor for long term safety of the products. This strategy is also included in the European Union (EU) Risk Management Plans for the products. To meet these regulatory commitments for Ziagen® (Abacavir), Kivexa® (Abacavir/lamivudine), Trizivir® (Abacavir/lamivudine/Zidovudine), Combivir® (Zidovudine/lamivudine), Telzir® (Fosamprenavir) and Celsentri® (Maraviroc), ViiV Healthcare in collaboration with the Data collection on Adverse events of anti-HIV Drugs (D:A:D) team, is conducting drug specific analyses of long term safety outcomes.

Objectives:

1. To describe any safety issues that arise among hepatically-impaired individuals exposed to Abacavir (ABC) containing products (Ziagen®, Kivexa®, Trizivir®) or Telzir®.
2. To determine the risk of carcinogenicity following exposure to Ziagen®, Kivexa®, Trizivir® and Combivir®.
3. To determine the risk of hepatotoxicity and ischaemic cardiac events following exposure to Celsentri®.
4. To determine the risk of hepatotoxicity and ischemic cardiac events in those exposed to Telzir®.

This will be a retrospective analysis of prospectively collected data from the D:A:D study which contains data from nearly 50,000 HIV-positive patients from 11 individual cohorts.

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Protocol Draft	15-March-2017
Registration on the EU PAS register	21-April-2017
Start of data analysis	22-April-2017
Draft report of study results	30-June-2017
Final report of study results	15-August-2017

6. BACKGROUND AND RATIONALE

6.1. Background

The D:A:D study has been investigating potential antiretroviral (ARV) drug toxicities since 1999 and is a multi-national collaboration made possible due to the pre-existence of several large well-established HIV cohorts in Europe, Australia and the United States. As of August 1st, 2016, the D:A:D cohort consisted of nearly 50,000 HIV-positive individuals with an accrued follow-up time of nearly 470,000 person years (PYRS) of follow-up from 11 individual cohorts.

Since the D:A:D study has been running, the cohort has developed a rigorous study methodology which includes the adoption of study-wide case-definitions, robust and reliable event ascertainment, central classification of key events (with the input of external experts), extensive data monitoring and a robust approach to statistical analyses. Over the years, the D:A:D study has also cooperated with and encouraged the wider research community to undertake confirmatory analyses and research on biological mechanisms. The long experience of investigating potential associations between adverse events (AEs) and ARV drugs has enabled the study to provide guidance on the routine use of ARV drugs in clinical practice.

Because of its observational nature, there are challenges with analyses of clinical endpoints which result from the multiple drug switches and the wide variety of ARV combinations in use at any time. Further complexities are introduced through the

necessity to adjust for potential confounders, and the need to consider the possibility that HIV and/or the immunodeficiency that results from this may also be an underlying or contributing cause of several outcomes. The aim of the D:A:D study has always been, and will continue to be, to explore clinically relevant associations between exposure to combination antiretroviral therapy (cART) and centrally validated clinical events in a timely manner while, as far as possible, taking into consideration the impact of both measured and unmeasured confounders.

6.2. Rationale

ViiV Healthcare's pharmacovigilance strategy for the mature product portfolio is to monitor for long term safety of the products. This strategy is also included in the European Union (EU) Risk Management Plans for the products. To meet these regulatory commitments for Ziagen® (Abacavir), Kivexa® (Abacavir/lamivudine), Trizivir® (Abacavir/lamivudine/Zidovudine), Combivir® (Zidovudine/lamivudine), Telzir® (Fosamprenavir) and Celsentri® (Maraviroc), ViiV Healthcare in collaboration with the D:A:D: team, is conducting drug specific analyses of long term safety outcomes.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Specific Aims:

1. To describe any safety issues that arise among hepatically-impaired individuals exposed to ABC containing products (Ziagen®, Kivexa® or Trizivir®) and Telzir®.
2. To determine the risk of carcinogenicity following exposure to Ziagen®, Kivexa®, Trizivir® and Combivir®.
3. To determine the risk of hepatotoxicity and ischaemic cardiac events following exposure to Celsentri®.
4. To determine the risk of hepatotoxicity and ischaemic cardiac events in those exposed to Telzir®.

1. Ziagen®, Kivexa®, Trizivir®: Potential risk: Carcinogenicity, Ischaemic cardiac events and Use in patients with hepatic impairment	**2. Celsentri®** Identified risk: Hepatotoxicity Potential risk: Ischaemic cardiac events
3. Combivir® Potential risk: Carcinogenicity	**4. Telzir®** Identified risk: Ischaemic cardiac events , Hepatotoxicity and Use in patients with hepatic impairment

8. RESEARCH METHODS

8.1. Study design

This is a retrospective analysis of prospectively (exposure data collected before outcome is known) collected data from the D:A:D study.

8.2. Study population and setting

Aim 1: All D:A:D participants who have evidence of co-infection with hepatitis B virus (HBV)/ hepatitis C virus (HCV) and/or chronic liver enzyme elevations (CLEEs) at the time of initiating one of the three treatments/combinations will be included. D:A:D collects data on alanine transaminase (ALT), AST, total bilirubin, platelet counts, albumin, creatinine, and haemoglobin and a host of other laboratory testing. Participants from cohorts that do not provide information on ALT levels will be excluded and CLEEs will be defined as in the recent D:A:D paper by Kovari et al. (1). The study population will therefore be split into three groups at the time of initiation of each treatment/combination: (i) those with HCV and/or HBV infection and no CLEE; (ii) those with no HCV and/or HBV but with CLEE; and (iii) those with HCV and/or HBV and CLEE. Due to the estimated small number of study participants with chronic hepatic impairment and/or CLEE, and the possibility that the antiretroviral drugs may themselves induce hepatic impairment or liver enzyme elevation, the groups will be defined at the time of first exposure to the treatment/combination and will not be updated if an individual's status changes (e.g. if his/her ALT levels fall or if the individual subsequently becomes co-infected with HCV/HBV). Participants whose first ALT level in the dataset post-dates the start of the treatment/combination will be excluded. Where possible, dosing levels will be captured for the hepatically-impaired individuals for the relevant products.

Aim 2: All D:A:D participants without a prior cancer at D:A:D study enrolment who are enrolled from cohorts that provide data on cancer incidence will be included. Individuals who have died or are lost-to-follow-up before the cohort-specific baseline date for cancer analyses (2004 onwards) will be excluded.

Aims 3 and 4: All D:A:D participants without liver impairment (hepatotoxicity includes end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and CLEE) or without a prior myocardial infarction (MI) at D:A:D study entry. Analyses of liver impairment will additionally exclude those from cohorts that do not provide data on ALT levels.

8.3 Variables

8.3.1. Exposure definitions

The D:A:D study does not capture information on specific co-formulations. Therefore, participants exposed to Trizivir®, Kivexa®, Ziagen® and Combivir® will be identified as follows:

Trizivir®: Any person whose current regimen includes ABC, lamivudine (3TC) and

zidovudine (AZT), regardless of other drugs in the regimen.

Kivexa®: Any person whose current regimen includes ABC and 3TC but not AZT, regardless of other drugs in the regimen.

Ziagen®: Any person whose current regimen includes ABC but not 3TC or AZT, regardless of other drugs in the regimen.

Combivir®: Any person whose current regimen includes AZT and 3TC but not ABC, regardless of other drugs in the regimen.

This will ensure that at any point in time, individuals can only be assigned to one of the four combinations (although individuals may switch from one of the combinations to another over time). Due to the very small number of persons exposed to Celsentri® and Telzir®, exposure to these drugs will be considered as any exposure, regardless of other drugs in the regimen.

8.3.2 Outcome definitions

Aim 1: Safety events will include:

- Clinical liver events (ESLD or HCC)
- Any cardiovascular CVevent (MI, invasive cardiovascular procedures (ICPs), sudden cardiac death, or stroke)

- Diabetes
- Cancer
- End-stage renal disease (ESRD)
- Mortality events

Aim 2: Cancer events will include:

- Any malignancy
- Any AIDS-defining malignancy (ADM)
- Kaposi's sarcoma (men only)
- Non-Hodgkin's lymphoma
- Cervical cancer (women only)
- Any non-AIDS-defining malignancy (NADM)
- Lung cancer
- Anal cancer (men only)
- Hodgkin's lymphoma
- Head and neck cancer

Aims 3 and 4: Hepatotoxicity and ischaemic cardiac events will include:

- Clinical liver endpoint: ESLD/HCC
- Laboratory-defined liver endpoint: CLEE
- MI

- Composite endpoint of MI or sudden cardiovascular death

In addition, assessment for hepatotoxicity will aim:

- To estimate the incidence of cases of combined alanine aminotransferase (ALT) and total bilirubin liver chemistry test elevations
- To estimate the incidence of discontinuation due to liver chemistry test elevations among exposed treatment naïve and treatment experienced HIV patients
- To determine risk factors for liver chemistry test elevations

Hepatic dysfunction as indicated by liver chemistry tests (LCT) will include the following, with a focus on alanine aminotransferase elevations and total bilirubin elevations:

- ALT elevations (ALT is also called serum glutamic pyruvic transaminase (SGPT))
- AST elevations (AST is also called serum glutamic oxaloacetic transaminase (SGOT))
- Alkaline phosphatase (ALP) elevations
- Total bilirubin elevations
- Albumin
- For hepatic disease additional data collected→ possible biopsy, fibroscan and signs of hepatic decompensation (Ascites, Hepatorenal syndrome, Spontaneous bacterial peritonitis, Hepatic encephalopathy grade 3 or 4, Oesophageal variceal bleeding)

8.4 Data sources

D:A:D is a prospective, observational multi-cohort study that focuses on the early recognition of AEs, amongst which are cardiovascular events, cancers, and liver and renal diseases that could result from HIV treatment with antiretroviral agents.

8.5 Study size

As of Merger 17, the study has captured data from 49,706 HIV-positive persons with a total follow-up of 467,477 PYRS from 11 different cohorts. Among this cohort, the study has information on 5372 deaths, 1191 MIs, 2794 cancer events (877 AIDS-defining, 1917 non-AIDS defining), 2002 new diagnoses of diabetes, 569 strokes, 432 ESLD and 131 ESRD events. As not all events will contribute to all planned analyses, some of the analyses may be based on relatively small group sizes and thus analyses may be descriptive.

8.6 Data management

A full manual of operations (MOOP) and Standard Operating Procedures for the D:A:D study can be accessed on the D:A:D website PPD These provide full details of the data management procedures that are in place as well as formats for data submission.

8.6.1. Data handling conventions

See above.

8.6.2. Timings of assessment during follow-up

Patients are seen for D:A:D clinical assessment at least every 8 months (depending on clinical need). Each participating cohort submits an annual electronic dataset to the D:A:D Co-ordinating centre.

8.7 Data analysis

The analyses will be based on the 17th D:A:D data merger of August 2016.

Aim 1: As it is likely that these individual groups will be relatively small, analyses will be largely descriptive and will summarise any subsequent clinical liver events (ESLD or HCC) as well as any CV event (MI, ICPs, sudden cardiac death and stroke), diabetes, cancer, ESRD, or mortality events that occur. Where possible, dosing levels will be captured for the hepatically-impaired individuals for the relevant products.

Aim 2: Participants will be stratified according to their level of exposure to each of the four treatments/combinations (no exposure; 0-2 years; 2-4 years; 4-6 years; 6-8 years, 8-10 years and >10 years) and strata-specific event rates will be calculated for the following outcomes:

- Any malignancy
- Any ADM
- Kaposi's sarcoma (men only)
- Non-Hodgkin's lymphoma
- Cervical cancer (women only)
- Any NADM
- Lung cancer
- Anal cancer (men only)
- Hodgkin's lymphoma
- Head and neck cancer

These outcomes have been chosen as they have the largest number of events in the current dataset. Follow-up will be considered from the baseline date for the cancer analyses (the latest of D:A:D entry or the cohort-specific baseline date for cancer analyses) to the date of the first new cancer over prospective follow-up (for analyses of specific cancer types, follow-up will therefore be censored at the time of a competing cancer event).

Poisson regression will be used to estimate unadjusted relative rates for the different exposure categories. If the number of each event is sufficient we will additionally fit multivariable Poisson regression models with adjustment for age, gender (where appropriate), cohort, mode of HIV acquisition, ethnic group, calendar year, previous cancer, smoking status, HCV and HBV co-infection. Models will also include adjustment for other ARV drugs in the regimen (results will not be shown for these other drugs).

Aim 3: Participants will be stratified according to whether or not they have ever received, or are currently receiving, Celsentri®. As the total number of D:A:D study participants exposed to Celsentri® is small, and the duration of exposure is generally short, no further stratification will be undertaken for duration of exposure to the drug. Event rates will be calculated for the following outcomes:

- Clinical liver endpoint: ESLD/HCC
- Laboratory-defined liver endpoint: CLEE (as defined above)
- MI
- Composite endpoint of MI or sudden cardiovascular death

As the number of events is expected to be small, no formal analyses will be undertaken, although the characteristics of those experiencing these events will be summarised.

Aim 4: Analyses will be similar to those described for Aim 3, although there will be some scope to stratify exposure to Telzir® (as none, <2 years, 2-4 years and ≥4 years). If the number of events is sufficient, we will perform Poisson regression to calculate relative rates for the exposure strata before and after adjustment for basic confounders (age and gender). Due to the limited exposure to the drug, we are unlikely to have sufficient numbers of events to be able to perform adjustment for other confounders.

8.8 Quality control and quality assurance

Please see D:A:D Study MOOP for quality control measures

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8.9 Limitations of the research methods

Whilst analyses will attempt to take account of any potential confounders, the observational nature of the study means that we are unable to rule out the possibility that unmeasured or unadjusted confounding may be present. This is particularly true of the proposed analyses which may include small numbers of participants and may be descriptive in nature. Thus, care should be taken when interpreting any findings to avoid making assumptions regarding causality.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Participating studies have existing national and/or local ethical approval, and obtain informed subject consent where required within these approvals.

9.2. Subject confidentiality

This analysis will use previously collected, anonymized data. No personal identifying information will be provided.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves retrospective analysis of previously collected data in an aggregate manner. There is no potential to collect serious and non-serious AEs, pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product.

Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target audience

The target audience includes regulatory and health authorities.

11.2. Study reporting and publications

Final study results will be included in safety and regulatory reports as appropriate. Study results can be published if the sample size is sufficient for detailed analysis.

12. REFERENCES

1. Kovari et al. Antiretroviral Drugs and Risk of Chronic Alanine Aminotransferase Elevation in Human Immunodeficiency Virus (HIV)-Monoinfected Persons: The Data Collection on Adverse Events of Anti-HIV Drugs Study. Open Forum Infect Dis. 2016 Jan 21; 3(1).

SPONSOR SIGNATORY:

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Vani Vannappagari PPD
Primary Author/ Project officer

6 APRIL, 2017
Date

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Harmony Garges PPD
VP, Global Medical Sciences

4/11/17
Date

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Nassrin Payvandi
VP, Safety and Pharmacovigilance

12/4/17
Date

1. INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: Caroline Sabin

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Investigator Signature

19/4/2017

Date

Investigator Name: Lene Ryom

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Date

Investigator Name: David Kamara

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Investigator Signature

4/5/2017

Date

Investigator Name: Camilla Hatleberg

Investigator Signature

Date

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Investigator Name: Caroline Sabin

Investigator Signature	Date

Investigator Name: Lene Ryom

PPD Investigator Signature PP D	19.04.2017 Date

Investigator Name: David Kamara

Investigator Signature	Date

Investigator Name: Camilla Hatleberg

Investigator Signature	Date

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Investigator Name: Lene Ryom

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Investigator Name: David Kamara

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Investigator Signature Date

Investigator Name: Camilla Hatleberg

PPD

_____ April 19, 2017

Investigator Signatu PPD Date

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