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Cryptococcus neoformans Infections Differ Among Human Immunodeficiency Virus (HIV)–Seropositive and HIV–Seronegative Individuals: Results From a Nationwide Surveillance Program in France

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Among 1107 cryptococcosis cases from the French surveillance network (2005–2020), the proportion of HIV-seronegative individuals has recently surpassed that of HIV-seropositive individuals. We observed marked differences in patient characteristics, disease presentations, cryptococcal antigen results, infecting species, and mortality according to HIV serostatus.

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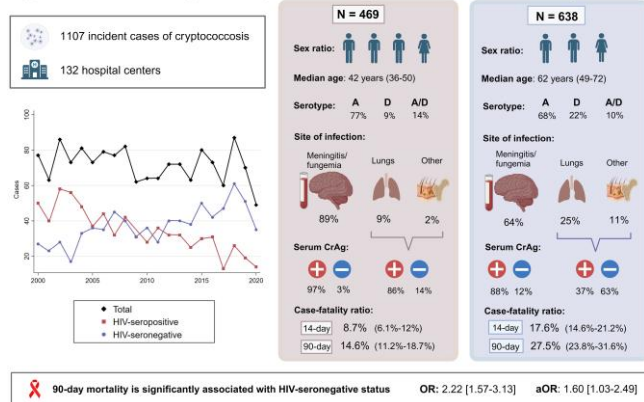
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Graphical Abstract

Cryptococcosis, France (2005-2020)



Keywords. cryptococcal meningitis; cryptococcosis; fungemia; human immunodeficiency virus.

Cryptococcosis is an opportunistic fungal infection that causes significant morbidity and mortality in immunocompromised hosts. Predisposing factors are T-cell immunodeficiencies mostly associated with advanced human immunodeficiency virus (HIV), but other risk groups such as solid-organ transplant recipients, patients with malignancy, and those receiving various immunosuppressive treatments or biologics constitute an increasing proportion of reported cases in North America and Europe [1–3] and up to 90% in Australia and New Zealand [4]. Differences in patient characteristics and outcomes have been reported among HIV-seropositive and HIV-seronegative individuals in population-based studies and single-center studies in North America [2, 5, 6], but precise multicenter data from Europe are lacking. We sought to describe the baseline characteristics, presentations, and outcomes of cryptococcosis according to HIV serostatus in France.

METHODS

We performed a cross-sectional study nested within a nationwide laboratory-based surveillance network for cryptococcosis in France (including overseas departments and territories) implemented in 1985 by the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA, Institut Pasteur, Paris, France). All isolates received were identified to the species level [7], and clinical data were monitored and stored at the NRCMA.

We included patients with incident microbiologically confirmed cryptococcosis from 1 January 2005 to 31 December 2020, and excluded cases caused by *Cryptococcus gattii* species complex (n = 20), isolated cryptococcal antigenemia, and recurrent cases. Cases of cryptococcosis were defined as illness in an individual with culture yielding growth of *Cryptococcus neoformans*

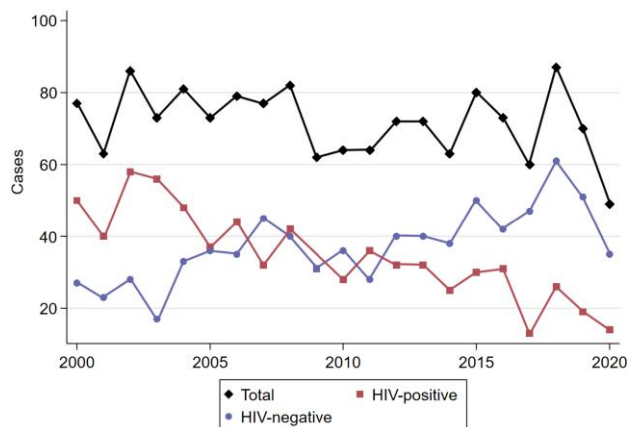


Figure 1. Number of cases reported to the NRCMA over time according to underlying HIV status, France.

species complex from any site, or with a positive cryptococcal antigen result (CrAg) from cerebrospinal fluid (CSF). For CSF, positive culture and/or a positive CrAg defined meningitis, while positive blood culture defined fungemia. In the absence of cryptococcal meningitis (CM)/fungemia, including when a lumbar puncture and/or blood culture had not been performed, cases were defined as isolated extrameningeal infections.

We compared baseline characteristics, disease presentations, and 14- and 90-day case fatality ratios (CFR) according to HIV serostatus. We compared categorical variables between groups using the χ^2 test or Kruskal-Wallis test and reported unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) using univariable logistic regression, taking into account only patients with available data. We used a multivariable logistic regression model to examine the association between HIV serostatus and 14- and 90-day mortality, adjusting for age (<50 and \geq 50 years), sex, site of infection (CM/fungemia, isolated pulmonary infections, or other isolated extrameningeal infections), and induction treatment regimen (flucytosine-containing regimen, other treatment regimen, or no treatment). Analyses were performed using Stata version 17 software (StataCorp, College Station, Texas). NRCMA surveillance activities were approved by the Institut Pasteur Institutional Review Board 1 (2009–34/IRB) and the Commission Nationale de l'Informatique et des Libertés. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.

RESULTS

We included 1107 incident cases of *C. neoformans*-related infections from 132 centers throughout France. Over the study period, while the total annual number of cases remained stable, the proportion of HIV-seropositive individuals decreased and that of HIV-seronegative individuals increased, eventually

Table 1. Baseline Characteristics and Outcomes According to Human Immunodeficiency Virus Serostatus Among 1107 Individuals With *Cryptococcus neoformans*-Related Infections in France, 2005–2020

Variable	Total (N = 1107)	HIV Seropositive (n = 469)	HIV Seronegative ^a (n = 638)	P Value
Age, y, median (IQR)	51 (39–65)	42 (36–50)	62 (49–72)	<.0001
Male sex	759/1107 (68.6)	357/469 (76.1)	402/638 (63)	<.001
Site of infection				<.001
Meningitis/fungemia	821/1107 (74.2)	417/469 (88.9)	404/638 (63.3)	
Isolated pulmonary	202/1107 (18.3)	42/469 (9)	160/638 (25.1)	
Other isolated site	84/1107 (7.6)	10/469 (2.1)	74/638 (11.6)	
LP performed	835/1107 (75.4)	428/469 (91.3)	407/638 (63.8)	<.001
Positive LP	623/1107 (56.3)	346/469 (73.8)	277/638 (43.4)	<.001
Blood culture performed	766/1107 (69.2)	356/469 (75.9)	410/638 (64.3)	<.001
Positive blood culture	480/1107 (43.4)	261/469 (55.7)	219/638 (34.3)	<.001
Pulmonary specimen obtained	442/1107 (39.9)	182/469 (38.8)	260/638 (40.8)	.54
Positive pulmonary culture	316/1107 (28.6)	113/469 (24.1)	203/638 (31.8)	.006
Urine culture obtained	433/1107 (39.1)	179/469 (38.2)	254/638 (39.8)	.62
Positive urine culture	137/1107 (12.4)	64/469 (13.7)	73/638 (11.4)	.31
Skin specimen obtained	104/1107 (9.4)	29/469 (6.2)	75/638 (11.8)	.002
Positive skin culture	85/1107 (7.7)	17/469 (3.6)	68/638 (10.7)	<.001
Serum CrAg results				
Serum CrAg performed	880/1035 (85)	405/442 (91.6)	475/593 (80.1)	<.001
Positive CrAg	722/880 (82.1)	388/405 (95.8)	334/475 (70.3)	<.001
Positive CrAg (cases of meningitis/fungemia only)	626/675 (92.7)	352/362 (97.2)	274/313 (87.5)	<.001
Positive CrAg (cases of isolated extrameningeal infections only)	96/205 (46.8)	36/43 (83.7)	60/162 (37)	<.001
<i>C. neoformans</i> complex serotype				<.001
<i>C. neoformans</i> (serotype A)	734/1021 (71.9)	336/435 (77.2)	398/586 (67.9)	
<i>C. deneoformans</i> (serotype D)	169/1021 (16.6)	39/435 (9)	130/586 (22.2)	
Serotype AD hybrid	118/1021 (11.6)	60/435 (13.8)	58/586 (9.9)	
Induction antifungal therapy				
Overall				<.001 ^b
5FC combination therapy	618/1076 (57.4)	322/457 (70.5)	296/619 (48.0)	
Including a polyene	598/1076 (55.6)	316/457 (69.1)	282/619 (45.6)	
AmB + 5FC	274/1076 (25.5)	170/457 (37.2)	104/619 (16.8)	
L-AmB + 5FC	324/1076 (30.1)	146/457 (32)	178/619 (28.8)	
Fluconazole + 5FC	20/1076 (1.9)	6/457 (1.3)	14/619 (2.3)	
Other treatment regimen	342/1076 (31.8)	120/457 (26.3)	222/619 (35.9)	
AmB monotherapy	31/1076 (2.9)	19/457 (4.2)	12/619 (1.9)	
L-AmB monotherapy	53/1076 (4.9)	16/457 (3.5)	37/619 (6)	
Fluconazole monotherapy	235/1076 (21.8)	74/457 (16.2)	161/619 (26)	
AmB and fluconazole	5/1076 (0.5)	4/457 (0.9)	1/619 (0.2)	
L-AmB and fluconazole	6/1076 (0.6)	5/457 (1.1)	1/619 (0.2)	
Other	12/1076 (1.1)	2/457 (0.4)	10/619 (1.6)	
No antifungals prescribed	116/1076 (10.8)	15/457 (3.3)	101/619 (16.3)	
Recorded as postmortem diagnosis	31/1076 (2.9)	3/457 (0.7)	28/619 (4.5)	
For cases of cryptococcal meningitis/fungemia only				<.001 ^b
5FC combination therapy	571/790 (72.3)	306/401 (76.3)	265/389 (68.1)	
Including a polyene	563/803 (70.1)	305/407 (74.9)	258/396 (65.2)	
AmB + 5FC	262/803 (32.6)	164/407 (40.3)	98/396 (24.8)	
L-AmB + 5FC	301/803 (37.5)	141/407 (34.6)	160/396 (40.4)	
Fluconazole + 5FC	18/803 (2.2)	5/407 (1.2)	13/396 (3.3)	
Other treatment regimen	160/790 (20.3)	82/401 (20.5)	78/389 (20.1)	
AmB monotherapy	27/803 (3.4)	18/407 (4.4)	9/396 (2.3)	
L-AmB monotherapy	32/803 (4)	13/407 (3.2)	19/396 (4.8)	
Fluconazole monotherapy	43/803 (11.6)	43/407 (10.6)	50/396 (12.6)	
AmB and fluconazole	4/803 (0.5)	3/407 (0.7)	1/396 (0.3)	
L-AmB and fluconazole	5/803 (0.6)	5/407 (1.2)	0/396 (0)	
Other	2/803 (0.3)	2/407 (0.5)	0/396 (0)	
AmB monotherapy	27/803 (3.4)	18/407 (4.4)	9/396 (2.3)	

Table 1. Continued

Variable	Total (N = 1107)	HIV Seropositive (n = 469)	HIV Seronegative ^a (n = 638)	P Value
No antifungals prescribed	59/790 (7.5)	13/401 (3.2)	46/389 (11.8)	
Recorded as postmortem diagnosis	29/59 (49.2)	3/13 (23.1)	26/46 (56.5)	
14-d CFR	128/899 (14)	33/380 (8.7)	95/535 (17.8)	<.001
90-d CFR	200/899 (22.3)	54/369 (14.6)	146/530 (27.6)	<.001

Data are presented as no./No. (%) unless otherwise indicated. Differences in denominators within each row reflect missing data.

5FC, flucytosine; AmB, amphotericin B; CFR, case fatality ratio; CrAg, cryptococcal antigen; HIV, human immunodeficiency virus; IQR, interquartile range; L-AmB, liposomal amphotericin B; LP, lumbar puncture.

^aIncluding 130 solid organ transplant recipients, 206 individuals with malignancy, 203 with other immunocompromising conditions, and 99 with no identified underlying factor.

^bComparison of 5FC combination therapy versus other treatment regimen versus no antifungals prescribed.

surpassing that of HIV-seropositive individuals from 2010 onward (Figure 1).

The median age of patients was 51 years (interquartile range [IQR], 39–65), and 759 of 1107 (68.6%) were male (Table 1). The most common presentation was CM/fungemia (74.2% [821/1107]). Of 286 individuals considered to have isolated extrameningeal infections, 44.1% (126/286) had neither lumbar puncture nor blood culture results recorded. Of the 1107 individuals, 469 (42.4%) were HIV seropositive and 638 (57.6%) were HIV seronegative. The median CD4 T-cell count was 26 cells/μL (IQR, 8–60) for 442 of 469 HIV-seropositive individuals with available data. Of 638 patients considered to be HIV-seronegative, 631 (98.9%) had records of a negative HIV serological test result. Compared to HIV-seronegative individuals, HIV-seropositive individuals were younger (median, 42 years [IQR, 36–50] vs 62 years [IQR, 49–72], $P < .0001$), and more likely to be male (76.1% [357/469] vs 63% [402/638]; $P < .001$). HIV-seropositive individuals were more likely to present with CM/fungemia (88.9% [417/469] vs 63.5% [405/638]) and less likely to present with isolated pulmonary disease (9% [42/469] vs 24.9% [159/638]) or other isolated extrameningeal disease (2.1% [10/469] vs 11.6% [74/638]) ($P < .001$).

HIV-seropositive individuals were more likely to have infections caused by *C neoformans* (serotype A) (77.2% [336/435] vs 67.9% [398/586]) or serotype AD hybrids (13.8% [60/435] vs 9.9% [58/586]) and less likely to have infections caused by *Cryptococcus deneoformans* (serotype D) (9% [39/435] vs 22.2% [130/586]) ($P < .001$). *Cryptococcus deneoformans* infections remained more frequent among HIV-seronegative than among HIV-seropositive individuals when considering those with CM/fungemia (20.4% [76/372] vs 9.2% [36/393]; $P < .001$) or with extrameningeal infections (25.2% [54/214] vs 7.1% [3/42]; $P = .006$).

HIV-seropositive individuals were also more likely to have a positive serum CrAg result at diagnosis (95.8% [388/405] vs 70.3% [334/475]; $P < .001$). This stayed significant when considering only patients with CM/fungemia (97.2% [352/362] vs 87.5% [274/313]; $P < .001$) or those with isolated extrameningeal infections (85.7% [36/42] vs 37% [60/162]; $P < .001$).

Over the study period, the proportion of patients with CM/fungemia who were prescribed a flucytosine-containing regimen gradually increased for both HIV-positive individuals (2005–2009: 66.3% [110/166] vs 2010–2014: 80.5% [103/128] vs 2015–2020: 85.8% [97/113]; $P < .001$) and for HIV-seronegative individuals (2005–2009: 57.9% [62/107] vs 2010–2014: 64.4% [74/115] vs 2015–2020: 77.6% [135/174]; $P < .001$) (Supplementary Table). Among cases of CM/fungemia, HIV-seropositive individuals were nevertheless more likely to have received a flucytosine-containing treatment regimen than HIV-seronegative individuals (76.3% [306/401] vs 68.1% [265/389]) and less likely to have received no antifungals (3.2% [13/401] vs 11.8% [46/389]) ($P < .001$). In addition, the use of liposomal amphotericin B as opposed to conventional amphotericin B in association with flucytosine increased over time in HIV-seropositive individuals (2005–2009: 11.5% [19/166] vs 2010–2014: 33.6% [43/128] vs 2015–2020: 69.9% [79/113]) and in HIV-seronegative individuals (2005–2009: 16.8% [18/107] vs 2010–2014: 40% [46/115] vs 2015–2020: 55.2% [96/174]).

The crude 90-day CFR was 14.6% (95% CI, 11.2%–18.7%; 54/369) among HIV-seropositive individuals and 27.5% (95% CI, 23.8%–31.6%; 146/530) among HIV-seronegative individuals. For 899 individuals with available outcome data, the crude odds of death at 90 days among HIV-seronegative individuals were 2.22 times (OR, 2.22 [95% CI, 1.57–3.13]; $P < .001$) higher than among HIV-seropositive individuals. After adjustment, the odds of 14-day and 90-day mortality in HIV-seronegative patients were still respectively 1.70 times (adjusted OR, 1.70 [95% CI, .97–2.99]; $P = .06$) and 1.60 times (adjusted OR, 1.60 [95% CI, 1.03–2.49]; $P = .038$) higher compared to HIV-seropositive individuals.

DISCUSSION

In these data from a large nationwide surveillance program in France, HIV-seronegative individuals have currently surpassed HIV-seropositive individuals as the main underlying risk group among reported cases of *C neoformans*-related infections over 16 years. This is driven by a persistent decline in the annual

number of cases reported among HIV-seropositive individuals since the mid-1990s, paralleling the declining incidence of AIDS (but not of HIV seropositivity) in France [8], and a steady increase in the number of cases reported among HIV-seronegative individuals. This shift in the epidemiology of cryptococcosis is consistent with previously reported trends from population-based studies in France and the United States [1, 2].

We found marked differences in patient characteristics and disease presentations among patients according to HIV serostatus. HIV-seropositive individuals were younger and more likely to be male than HIV-seronegative individuals [2, 5, 6, 9]. CM/fungemia accounted for 89% of reported cases among HIV-seropositive individuals, compared to only 64% for HIV-seronegative individuals, who more frequently presented with isolated pulmonary and other isolated infections. Similar differences were previously reported, albeit with different definitions of dissemination [10]. In addition, infecting *C neoformans* complex species varied according to HIV serostatus, with HIV-seropositive individuals more likely to have infections caused by *C neoformans* and serotype AD hybrid while HIV-seronegative individuals were more likely to have *C deeneoformans* infections. These differences persisted when accounting for the fact that serotype D infections are more prevalent in primary cutaneous infections [9]. HIV-seropositive individuals were also more likely to have a positive serum CrAg test at baseline. Of note, 12.5% of HIV-seronegative patients with CM/fungemia had a negative serum CrAg compared to only 2.8% for HIV-seropositive individuals. This illustrates its poorer diagnostic contribution in HIV-seronegative populations, presumably reflecting a lower fungal burden among HIV-seronegative patients [9, 10]. Thus, it should be remembered that in clinical practice, a negative serum CrAg result does not exclude CM/fungemia among HIV-seronegative patients.

Of note, HIV-seronegative individuals experienced a 1.6 times higher mortality compared to HIV-seropositive individuals after adjustment. Differences in mortality rates can be attributed to (1) a delayed diagnosis linked to a lower index for suspicion in HIV-seronegative individuals, (2) decreased awareness of less typical disease presentations, (3) the prognosis of the underlying disease, and/or (4) the irreversibility of immunodepression among many HIV-seronegative individuals [2, 3].

Some limitations of our study are linked to the data collected at the NRCMA. For instance, we were not able to assess attributable mortality. In addition, important confounders of mortality, such as altered mental status and elevated opening pressure [11], were not routinely collected.

Our study nevertheless represents the first large cohort emphasizing that *Cryptococcus neoformans* is responsible for 2 different diseases according to HIV serostatus. It should serve as a reminder that the recent dramatic therapeutic improvements

obtained in HIV-associated cryptococcal meningitis patients should not necessarily be extrapolated to HIV-seronegative individuals [12]. As HIV-seronegative individuals comprise a heterogeneous group with a wide range of immunosuppressive backgrounds [3, 5, 6, 9, 10], there is a need for more in-depth research on cryptococcosis in this setting.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Writing—original draft: O. P. Writing—review and editing: M. D.-O., A. A., O. L., and F. L. Methodology: O. P., M. D.-O., and F. L. Data curation: M. D.-O., K. B.-S., A. A., S. C., C. B., J. B., F. B., M.-E. B., S. B., T. C., M. C., E. D., M. D., N. D.-N., M.-F. D., L. F., A. F., F. G., J.-P. G., J. G., L. H., A. H., S. L., V. L. B., C. M., L. M., F. M., M. N., C. R., E. P., F. P., P. P., S. R., G. R., A.-L. R., and M. S. Conceptualization: O. P., O. L., and F. L.

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CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS⁴⁻⁹

Treatment-naïve resistance rates, with up to **3 years** of evidence⁵⁻⁷

0%
(n=0/1,885)^{*4}
REAL-WORLD EVIDENCE

0.1%
(n=1/953)^{**1,11,11,11}
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years** of evidence¹⁻³

0.03%
(n=10/35,888)^{*4}
REAL-WORLD EVIDENCE

0%
(n=0/615)^{11,11,11,11}
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY¹⁰

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:^{4-9,11,11}



NO PRIOR TREATMENT EXPERIENCE¹³



NO BASELINE RESISTANCE TESTING¹³



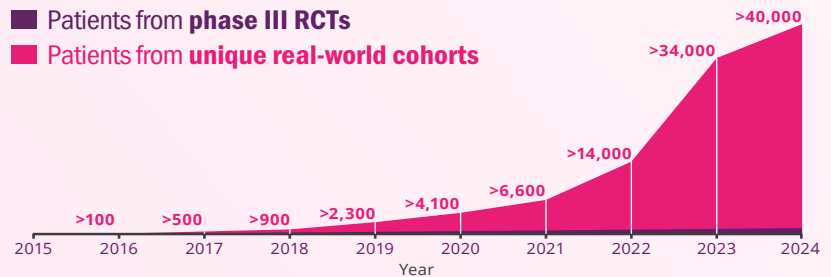
HIGH BASELINE VIRAL LOAD
(>100,000 copies/mL and even >1M copies/mL)^{6,13}



LOW CD4 + COUNT
(≤200 cells/mm³)¹³

■ Patients from phase III RCTs

■ Patients from unique real-world cohorts



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

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DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.¹³

Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

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ABBREVIATIONS

3TC, lamivudine; **CD4**, cluster of differentiation 4; **DTG**, dolutegravir; **FDA**, United States Food and Drug Administration; **FTC**, emtricitabine; **HIV**, human immunodeficiency virus; **ITT-E**, intention-to-treat exposed; **NRTI**, nucleoside/nucleotide reverse transcriptase inhibitor; **RCT**, randomised controlled trial; **RNA**, ribonucleic acid; **TAF**, tenofovir alafenamide fumarate; **TDF**, tenofovir disoproxil fumarate; **XTC**, emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).⁵⁻⁷

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).¹³

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.⁶

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.⁷ Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSAs (n=0/246, through 48 weeks).^{8,9}

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).^{8,13}

#SALSAs is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).⁹