A Double-Blind Comparison of Itraconazole Oral Solution and Fluconazole Capsules for the Treatment of Oropharyngeal Candidiasis in Patients with AIDS

Peter Phillips, Karel De Beule, Gervais Frechette, Stephan Tchamourloff, Bernard Vandercam, Lutwinus Weitner, Andy Hoepelman, Georg Stingl, and Buenaventura Clotet

This double-blind trial compared the clinical and mycological efficacy and safety of itraconazole oral solution with those of fluconazole capsules in the treatment of oropharyngeal candidiasis in patients with AIDS. A total of 244 patients were enrolled and randomized to one of three groups for treatment with itraconazole oral solution (100 mg twice daily for 7 days or 100 mg once daily for 14 days) or fluconazole capsules (100 mg once daily for 14 days). Among 194 evaluable cases, complete response (clearance of all symptoms and signs) or marked improvement was noted in 54 of 60 patients (90%) receiving once-daily itraconazole and in 65 of 72 fluconazole-treated patients (90%) at the end of treatment; these results were statistically equivalent (P = .0024). Twice-daily itraconazole produced a clinical response in 51 of 62 patients (82%). The groups were equivalent in terms of early relapse (within the 18-day period studied); 37% of patients in the twice-daily itraconazole group, 35% in the once-daily itraconazole group, and 34% in the fluconazole group relapsed. Drug tolerability was comparable between the three groups. These results show that, in the treatment of oropharyngeal candidiasis, itraconazole oral solution and fluconazole capsules at a 100-mg single daily dose for 14 days are equally effective.

Oropharyngeal candidiasis is the most frequently occurring opportunistic infection encountered in HIV-infected individuals [1, 2], affecting nearly all patients at some time during the course of the disease. Topical therapy for oropharyngeal candidiasis is relatively inexpensive and avoids potential systemic drug toxicity and interactions. However, relapses may be frequent, and systemic azole therapy (e.g., with ketoconazole, fluconazole, or itraconazole) is usually required for patients who are intolerant of or whose conditions are poorly controlled with nystatin, clotrimazole, or oral amphotericin B [3].

Although ketoconazole remains useful in AIDS-related oropharyngeal candidiasis, impaired absorption and drug interactions may sometimes lead to clinical failure. Fluconazole is usually administered at dosages of 100 mg daily for 7–14 days for oropharyngeal candidiasis [4]. However, daily or intermittent long-term suppressive fluconazole therapy to prevent frequent recurrences [5, 6] may result in the development of resistance to fluconazole. A marked increase in the number of fluconazole-resistant cases has recently been noted [7–12].

Itraconazole capsules have been registered for the treatment of oropharyngeal candidiasis in several countries and have been shown to be more effective than placebo and equivalent in efficacy to ketoconazole [13, 14]. The present study was designed to evaluate a new formulation of itraconazole, prepared as an oral solution with a hydroxypropyl-β-cyclodextrin vehicle. The solution formulation was developed to increase the absorption and salivary concentrations obtained with itraconazole capsules. Improved bioavailability would be of particular benefit in patients with AIDS, and the combination of systemic and topical effects of itraconazole oral solution may provide greater efficacy than the capsule formulation for this indication, yielding faster treatment responses (within 1–2 days) [15].

Previously, all 39 patients with oropharyngeal candidiasis treated with itraconazole oral solution (100 mg b.i.d. for 7 days) were clinically cured [16]. In the present double-blind study, the role of itraconazole oral solution in the treatment of HIV-related oropharyngeal candidiasis was investigated with use of two dosing schedules, 100 mg twice daily for 7 days and 100 mg once daily for 14 days, in comparison with fluconazole capsules (100 mg once daily for 14 days). The three treatment schedules provided the same total dose.
Methods

The study was conducted in 25 centers in seven countries (Austria, Belgium, Canada, Germany, the Netherlands, Spain, and the United Kingdom) between June 1993 and August 1994. All patients gave informed, signed consent before participating. The study protocol was approved by the investigational review boards of the participating institutions.

Patients enrolled in the trial were at least 19 years old, were HIV-infected, had a CD4 cell count of <400/mm³ documented within the previous month, and had pseudomembranous oropharyngeal candidiasis (with removable white plaques) including erythema or the symptoms of soreness or burning. Exclusion criteria included inability to take oral medication, systemic antifungal treatment within the previous 2 weeks or intraoral topical antifungal treatment within 1 week before the trial, hypersensitivity to oral azoles, candidiasis not responsive to fluconazole or itraconazole, suspicion of candidal esophagitis, liver dysfunction (alanine or aspartate aminotransferase level ≥5 times the upper limit of normal within 1 month before the trial), or estimated creatinine clearance of <50 mL/min. Concurrent use of terfenadine, astemizole, phenytoin, carbamazepine, phenobarbital, rifampin, oral anticoagulants, or sulfonylureas was not permitted during the trial.

At the first visit, the baseline assessment included a physical examination and recording of any history of oropharyngeal candidiasis, HIV risk factors, and concurrent medications. At each center, patients were randomized in blocks of 12 to one of the three treatment regimens, according to a predefined randomization code, ensuring that an equal number of patients were allocated to each treatment group. Because the study treatments consisted of capsules and oral solution, patients received fluconazole capsules (100 mg once daily for 14 days) with placebo oral solution or else itraconazole oral solution (either 100 mg once daily for 14 days [itraconazole o.d.] or 100 mg twice daily for 7 days [itraconazole b.i.d.] with placebo capsules). Active and placebo forms were provided by the Janssen Research Foundation and were blinded so that neither the investigators nor the patients were aware of their contents.

Patients were instructed to take 10 mL of solution (containing a 10-mg/mL concentration of itraconazole or placebo), preferably without a meal, twice daily (morning and evening), and one capsule daily for the first week; they then took one capsule and 10 mL of solution once daily for the second week. The solution was to remain in contact with the oral mucosa for at least 10 seconds before being swallowed. Compliance was monitored by the return of any unused medication. Treatment lasted for 14 days, and patients were followed up for a further 2 weeks to assess relapse.

Efficacy. Global clinical assessment was performed on day 8 (after 7 days of treatment) and day 15 (after 14 days of treatment) and at 1 and 2 weeks during the follow-up period, unless symptoms prompted assessment at another time. In cases of relapse between visits, the assessment was entered in the records for the closest corresponding visit and the exact date was indicated. Clinical assessment was based upon changes in the investigator’s rating of signs and symptoms. To facilitate the assessments, the severity of symptoms and signs (soreness/burning, dysphagia, erythema, and removable white plaques) were scored on a three-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Extent of the lesions was also scored (0 = no lesions, 1 = localized lesions, 2 = extensive lesions) and monitored with the assistance of oral-cavity diagrams for estimating lesion sizes and locations.

Patients kept a daily diary of symptoms. Since the scoring system has not been formally validated, clinical responses were based upon the investigators’ overall assessment but did not depend upon achievement of a specific score for signs and symptoms. Responses were classified as complete response (clearance of all symptoms and signs, except erythema) or markedly improved, moderately improved, unchanged, or deteriorated condition.

Mycologic assessment, on the basis of the presence or absence of fungal forms consistent with candidiasis in the oral scrapings, was performed by microscopy (with KOH, gram, or methylene blue staining) and culture (with Sabouraud’s PS [penicillin/streptomycin] agar) at enrollment, on days 8 and 15, and at the time of any clinical recurrence. Follow-up microscopy or culture results that were missing were assumed to have been positive, unless otherwise stated. When posttreatment follow-up clinical assessments were missing, it was assumed that the patients had relapsed.

Safety. To assess safety, any adverse event mentioned by patients during the trial was noted, and hematologic and biochemical laboratory tests were performed on blood samples taken 24 hours before enrollment, on days 8 and 15 during the treatment period, and at the end of the 2-week follow-up period. Heart rate, blood pressure, and body temperature were measured at enrollment and on day 15. Patients were withdrawn from the study if they withdrew consent, if their oropharyngeal candidiasis worsened by day 8 (classified as treatment failure), or if any serious adverse event occurred.

Statistical analysis. To detect possible differences in baseline characteristics between the treatment groups, continuous data were subjected to the Kruskal-Wallis test. Nominal categorical data (e.g., sex) were subjected to Fisher’s exact test. The efficacy parameters were tested for equivalence between the treatment groups. In this analysis, only evaluable patients were included, whereas all patients for whom data were available were included in the safety analysis.

The Blackwelder test [17] was used for clinical response, with application of the procedure for two one-sided tests: a first P value was calculated for the null hypothesis that the response with itraconazole is greater than with fluconazole by at least 15%. A second P value was calculated for the null hypothesis that the response with fluconazole is at least 15% greater than with itraconazole. If both P values are <.0125, then equivalence between the two treatments is proven. The
Table 1. Baseline characteristics of patients with oropharyngeal candidiasis treated with itraconazole or fluconazole.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Patients enrolled (no.)</td>
<td>79</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>9:11</td>
</tr>
<tr>
<td>Unevaluable (no. of patients), because of</td>
<td>17</td>
</tr>
<tr>
<td>Negative culture</td>
<td>8</td>
</tr>
<tr>
<td>Negative or missing microscopy result</td>
<td>6</td>
</tr>
<tr>
<td>No follow-up</td>
<td>3</td>
</tr>
<tr>
<td>No oral plaques</td>
<td>0</td>
</tr>
<tr>
<td>Evaluable patients (no.)</td>
<td>62</td>
</tr>
<tr>
<td>Years of age, median (range)</td>
<td>36 (25–64)</td>
</tr>
<tr>
<td>Weight in kg, median (range)</td>
<td>66 (48–101)</td>
</tr>
<tr>
<td>Present episode a relapse (no. of patients)</td>
<td>30</td>
</tr>
<tr>
<td>No. of CD4 cells/mL, mean (SEM)</td>
<td>151 (27)</td>
</tr>
</tbody>
</table>

* Patients were randomized to receive itraconazole oral solution (100 mg b.i.d. for 7 days or 100 mg once daily [o.d.] for 14 days) or fluconazole capsules (100 mg once daily for 14 days).

Results

Patients. A total of 244 patients were recruited, of whom 194 were evaluable. Baseline characteristics, including reasons for patients being unevaluable, are summarized in table 1. Body weight was lower in the itraconazole o.d. group ($P = .002$). There were no other significant differences between the three groups at study enrollment.

Clinical response. Clinical response to treatment is summarized in figure 1. A clinical response (i.e., complete response or marked improvement) was achieved in 51 (82%) of 62 evaluable itraconazole b.i.d. recipients, 54 (90%) of 60 itraconazole o.d. recipients, and 65 (90%) of 72 fluconazole recipients at the end of the treatment period. For the itraconazole o.d. and fluconazole treatments, these results were equivalent ($P = .0024$). The comparison between the itraconazole b.i.d. and fluconazole regimens did not reach statistical equivalence. There were clinical responses at day 7 of treatment in 78% of the itraconazole b.i.d. group and 88% of both the itraconazole o.d. and fluconazole groups.

The mean scores for symptoms and signs in each treatment group at study enrollment and after 14 days of treatment are shown in table 2. Eight patients were removed from the trial on day 8, in accordance with the protocol, because of worsening of oropharyngeal candidiasis (itraconazole b.i.d., four recipients; fluconazole, four recipients).

Mycologic examination. At the time of enrollment, all evaluable patients had positive microscopy and culture results. Most infections were caused by Candida albicans. Non-albicans Candida species or mixed infections were observed in 5%–10% of patients in each group (table 3). After 7 days of

Table 2. Clinical responses to treatment for oropharyngeal candidiasis: mean scores for signs and symptoms.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 62)</td>
</tr>
<tr>
<td>Extent of lesions</td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>1.19</td>
</tr>
<tr>
<td>On day 14*</td>
<td>0.30</td>
</tr>
<tr>
<td>White plaques</td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>1.66</td>
</tr>
<tr>
<td>On day 14*</td>
<td>0.19</td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>1.67</td>
</tr>
<tr>
<td>On day 14*</td>
<td>0.34</td>
</tr>
<tr>
<td>Soreness/burning</td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>1.27</td>
</tr>
<tr>
<td>On day 14*</td>
<td>0.04</td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>At enrollment</td>
<td>0</td>
</tr>
<tr>
<td>On day 14*</td>
<td>0.04</td>
</tr>
</tbody>
</table>

See Methods for explanations of the treatment regimens and scoring systems.

* Day 14 scores were missing for 30 patients: itraconazole b.i.d., 9 recipients (clinical response, 4 of 9); itraconazole o.d., 13 recipients (clinical response, 11 of 13); and fluconazole, 8 recipients (clinical response, 5 of 8).

† Enrollment scores for dysphagia were missing for 10 patients: itraconazole b.i.d., 3 recipients; itraconazole o.d., 4 recipients; and fluconazole, 3 recipients.
Table 3. Candida isolates recovered at baseline from evaluable patients with oropharyngeal candidiasis.

<table>
<thead>
<tr>
<th>Candida species recovered</th>
<th>Itraconazole b.i.d.</th>
<th>Itraconazole o.d.</th>
<th>Fluconazole</th>
<th>No. of patients per treatment group*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>(n = 62)</td>
<td>(n = 60)</td>
<td>(n = 72)</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans + C. glabrata</em></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans + C. tropicalis</em></td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans + Saccharomyces cerevisiae</em></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>C. albicans + C. krusei</em></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Unidentified <em>Candida species</em></td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* Patients were randomized to receive itraconazole oral solution (100 mg b.i.d. for 7 days or 100 mg once daily [o.d.] for 14 days) or fluconazole capsules (100 mg once daily for 14 days).

Table 4. Adverse events during treatment for oropharyngeal candidiasis.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Itraconazole b.i.d.</th>
<th>Itraconazole o.d.</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>5</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Liver enzyme level or function anomalies</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Taste perversion or anorexia</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Coma</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Convulsion</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>26 (33)</td>
<td>38 (48)</td>
<td>37 (43)</td>
</tr>
</tbody>
</table>

* Other adverse events occurring in <2% of patients in each group included fatigue, syncope, dizziness, weight loss, pruritus, toxoplasmosis, hyperglycemia, hyperuricemia, and hyponatremia. *Pneumocystis carinii* pneumonia, cough, and bacterial infections occurred in <3% of patients in each group.

Relapse. The clinical relapse rates within 18 days were 37% in the itraconazole b.i.d. group (19 of 51 responders), 35% in the itraconazole o.d. group (19 of 54 responders), and 34% in the fluconazole group (22 of 65 responders). The numbers of responders who missed follow-up assessments and were assumed to have relapsed were 13, 12, and 14 in each group, respectively. Among the minority of patients at the end of the follow-up period for whom results of culture and microscopy were available, cultures were negative for 13 (62%) of 21 patients in the itraconazole b.i.d. group, 8 (53%) of 15 patients in the itraconazole o.d. group, and 15 (48%) of 31 patients in the fluconazole group. Similarly, microscopy results were negative for 5 of 17 (29%), 5 of 12 (42%), and 9 of 27 patients (33%) in each group, respectively.

Safety. All 244 patients were included in the adverse-event analysis. Of these, 242 patients had completed all toxicity-related laboratory tests. No differences in the frequency of adverse events were noted between the three treatment groups (33% in the itraconazole b.i.d. group, 48% in the itraconazole o.d. group, and 43% in the fluconazole group). Gastrointestinal symptoms, mostly diarrhea and nausea, were the most frequently reported adverse events during treatment (table 4). The underlying disease or concomitant medications may have accounted for a significant proportion of the adverse events.

No consistent changes in mean values of blood hematology and biochemistry or urinary parameters were noted, despite...
numerous individual abnormalities in laboratory parameters in all three treatment groups (table 4). Abnormalities in a total of 183 patients were recorded during the treatment period (itraconazole b.i.d., 62; itraconazole o.d., 54; and fluconazole, 67). The frequency of abnormalities was considered to be representative of the pattern of the underlying disease in these patients.

Discussion

The results of the present study show that in the treatment of HIV-related oropharyngeal candidiasis, a single daily 100-mg dose of itraconazole oral solution is as effective as a once-daily 100-mg dose of fluconazole, when each is given for 14 days. The two treatment regimens both showed a high clinical response rate of 90%. Treatment with itraconazole b.i.d. for 7 days was not as effective as the other two regimens but still produced an acceptable clinical response rate of 82%. The relapse rates and time to early relapse were similar for the three treatment regimens during the 2 weeks after the end of treatment. The microscopic cure rates were somewhat lower than the clinical response rates in all three treatment groups, although the clinical significance of this observation is unclear.

Our results are consistent with those of a similar study conducted by Graybill et al. [18]. The three treatment regimens in that study were as follows: itraconazole oral solution, 200 mg daily for 7 days; itraconazole, 200 mg daily for 14 days; and fluconazole, 100 mg daily for 14 days. These were associated with success rates of 83%, 97%, and 87%, respectively. The response rate was lower with the 7-day itraconazole regimen in both studies but was unexplained in our trial, given the same total dose was administered in the 7-day and 14-day itraconazole groups.

Using an antifungal agent in an oral solution, which contacts the oral mucosa before being ingested, offers systemic treatment and probably an important topical effect not provided by the itraconazole capsule formulation. Whether or not a minimum contact time of longer than 10 seconds before swallowing would have improved efficacy in this study is speculative. In a recent study, Reynes et al. [19] demonstrated sustained itraconazole concentrations for 8 hours in the saliva of patients receiving itraconazole oral solution for HIV-related oropharyngeal candidiasis. The absence of hydroxyitraconazole, a metabolite of itraconazole, in saliva suggested that the salivary drug concentrations were not the result of salivary excretion of systemically absorbed drug.

Another advantage of the oral solution, particularly relevant to the treatment of AIDS patients, is its improved bioavailability, since its absorption is as much as 60% greater than that of the capsule formulation (unpublished data). Despite its somewhat bitter taste, itraconazole solution may be easier to swallow than capsules or pills, particularly for patients with significant dysphagia or odynophagia.

In addition, itraconazole oral solution may be useful in cases of fluconazole-resistant mucosal candidiasis. In vitro susceptibility tests suggest that not all fluconazole-resistant strains of Candida are cross-resistant to itraconazole [20, 21], and recent reports have indicated favorable responses (60-80%) in fluconazole-resistant cases treated with itraconazole oral solution (200–400 mg daily) [22–24].

Conclusion

Itraconazole oral solution at a dosage of either 100 mg once daily for 14 days or 100 mg twice daily for 7 days is an effective first-line treatment for oropharyngeal candidiasis, although the 14-day regimen is more effective. Itraconazole oral solution and a fluconazole regimen of 100 mg once daily for 14 days are therapeutically equivalent in the treatment of oropharyngeal candidiasis. These antifungal agents appear to be equally well tolerated. Adverse events and laboratory abnormalities occurred frequently in all three treatment groups during the present study.

Acknowledgments

Investigators participating in the present study included the following.

Austria: J. Aubock and M. Geit, Department of Dermatology, General Hospital, Linz; A. Geusau and F. Hladik, University Department of Dermatology, Vienna; and N. Vetter, Municipal Pulmonary Center, Vienna.

Canada: J. Baril and R. Laroche, Medical Clinic Mont Carmel, Montreal; C. Tsoukas, J. Falutz, M. Harris, and J. Szabo, Montreal General Hospital, Montreal; W. Schleich, Victoria General Hospital, Halifax; S. Walmsley, Toronto General Hospital, Toronto; and J. Epstein, British Columbia Cancer Agency, Vancouver.

Germany: E. Baranowski, private practice, Berlin; H. Holzhuter, private practice, Bremen; H. Jürgen-Lohman, private practice, Frankfurt; H. Kreutzman, private practice, Bremen; X. Olbricht, University Clinic, Essen; X. Pfeil, University Clinic, Leipzig; M. Ruhnke, Rudolf Virchow Clinic, Berlin; and D. Schuster, private practice, Mannheim.

Netherlands: J. Borleffs, M. Schneider, and W. Hustinx, University Hospital, Utrecht.

United Kingdom: J. Cartledge, B. Gazzard, and D. Hawkins, Westminster Hospital, London; M. Johnson, Royal Free Hospital, London; S. Kumar and M. Newell, Royal Sussex County Hospital, Brighton; and P. Woolley, Withington Hospital, Manchester.

Spain: R. Llamas and C. Zarco, Hospital 12 Octubre, Madrid.

References


Please excuse the presence of this and the following test pages, which have been added to a small number of article PDFs for a limited time as part of our process of continual development and improvement.
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod
tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim
veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea
commodo consequat. Duis aute irure dolor in reprehenderit in volup
tate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat
 cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id
est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed
do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim
ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut
enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip
ex ea commodo consequat. Duis aute irure dolor in reprehenderit in
voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint
occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit
anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing
elit, sed do
Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.